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# Posttraumatic Stress Disorder or Combat Experience? A Functional Near-infrared Spectroscopy Study of Trauma-related Auditory and Olfactory Cues

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# POSTTRAUMATIC STRESS DISORDER OR COMBAT EXPERIENCE? A FUNCTIONAL NEAR-INFRARED SPECTROSCOPY STUDY OF TRAUMA-RELATED AUDITORY AND OLFACTORY CUES

by

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# ABSTRACT

While the clinical communities are aware of the prevalence of posttraumatic stress disorder (PTSD) among OEF/OIF/OND veterans, further efforts are necessary to bolster comprehensive strategies for assessment and treatment. The purpose of this study was to investigate whether a combat-related PTSD symptom provocation paradigm would elicit unique neurological responses via functional near-infrared spectroscopy across three groups – combat veterans with PTSD, combat veterans without PTSD, and nonmilitary participants without PTSD. Results indicated that combat veterans with PTSD demonstrated significant activation during exposure to a trauma-related sound compared to nonmilitary personnel at channels 14 ($d$ = 1.03) and 15 ($d$ = 1.30) and combat veterans without PTSD at channel 14 ($d$ = 0.87). Specifically, this increased neural activation was approximately located in the right superior/medial prefrontal cortex (BA 9/10), associated with evaluating cue-familiarity and emotional detachment. 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.

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| | |
|---|---|
| ACC | Anterior Cingulate Cortex |
| ATP | Adenosine Tri-Phosphate |
| BA | Broadmann Area |
| BOLD | Blood-Oxygenation Level Dependent |
| CAPS | Clinician-Administered PTSD Scale |
| CBF | Cerebral Blood Flow |
| DEOXY-HB | Deoxygenated Hemoglobin |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EEG | Electroencephalogram |
| EMG | Electromyogram |
| FDR | False Discovery Rate |
| FMRI | Functional Magnetic Resonance Imaging |
| FNIRS | Functional Near-Infrared Spectroscopy |
| IED | Improvised Explosive Device |
| MDD | Major Depressive Disorder |
| M-FAST | Miller Forensic Assessment of Symptoms Test |
| MINI | MINI International Neuropsychiatric Interview 6.0 Version |
| OEF | Operation Enduring Freedom |
| OIF | Operation Iraqi Freedom |
| OSU TBI-ID | Ohio State University Traumatic Brain Injury Identification Method |
| OXY-HB | Oxygenated Hemoglobin |
| PET | Positron Emission Tomography |

| | |
|---|---|
| PTSD | Posttraumatic Stress Disorder |
| SCID-II | Structured Clinical Interview for DSM-IV Personality Disorders, Personality Questionnaire |
| SCID-CV | Structured Clinical Interview for DSM-IV |
| SPM | Statistical Parametric Mapping |
| TBI | Traumatic Brain Injury |
| TSI | Trauma Symptom Inventory |
| UCF | University of Central Florida |
| UPSIT | University of Pennsylvania Smell Identification Test |
| VA | U.S. Department of Veterans Affairs |
| VMPFC | Ventromedial Prefrontal Cortex |

# CHAPTER 1: INTRODUCTION

Posttraumatic stress disorder (PTSD) diagnosis is substantial among United States military service men and women. Currently, clinicians rely primarily on diagnostic interviews and self-report measures. However, biological markers such as functional near-infrared spectroscopy (fNIRS) may offer additional benefits including improved diagnosis, determination of best course of treatment, objective markers of treatment outcome, and remission of the disorder (Lehrner & Yehuda, 2014; Takizawa et al., 2014). In addition, objective indicators may improve detection and direct available resources for those in need of treatment due to under reporting (e.g., desire to continue working in occupations that involve crisis management), as well as over reporting (e.g., cases involving compensation or litigation; Lehrner & Yehuda, 2014). An associated biological component may provide an additional patient characteristic that extends clinical utility to mental health care professionals diagnosing and treating PTSD in their daily practices (e.g., further confirmation of symptom severity and/or diagnosis). Presently, no validated biological assessment for PTSD is available.

## 1.1 PTSD

Since October 2001, over 2.7 million troops have deployed to Iraq or Afghanistan (U.S. Department of Veterans Affairs; VA, 2014a). According to the National Center for PTSD, the current prevalence rate among military personnel in a given year ranges from 10%–12% for Gulf War veterans and approximately 13% for Operation Enduring Freedom (OEF; Afghanistan) and Operation Iraqi Freedom (OIF; Iraq) veterans (Kang, Natelson, Mahan, Lee, & Murphy, 2003; Kok, Herrell, Thomas, & Hoge, 2012; Schell & Marshall, 2008). Moreover, point prevalence for combat-related PTSD has been estimated as high as 17% using samples of OEF/OIF veterans

(Hoge, et al., 2004; for review, see Richardson, Frueh, & Acierno, 2010). The 12-month prevalence rate for PTSD among adults in the U.S. ranges from 3.5%–4.4%, which consequently ranks PTSD as the fourth most common psychiatric disorder (Kessler et al., 2005; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Thus, military personnel are at a higher risk for developing PTSD in comparison to the general U.S. population (5th ed.; *DSM*-5; American Psychiatric Association, 2013). Despite efforts to screen military service men and women for physical and mental functioning, as well as executing training sessions to handle high-stress combat situations, a significant risk exists for developing PTSD among combat veterans (Litz, 2014).

Eibner, Ringel, Kilmer, Pacula, and Diaz (2008) estimated the associated costs of PTSD and major depressive disorder (MDD) over a two-year period following discharge for 1.6 million troops returning from OEF/OIF deployments since 2001. The total costs for PTSD alone estimated to $688 million, which equates to approximately $5,904 per military member. Veterans with comorbid PTSD and MDD reached a separate total of $1.5 billion or approximately $12,427 per case. The total cost estimates of PTSD and MDD projected that 94.5% were linked to productivity loss (e.g., reduced employment and lower earnings), while only 5.1% were attributable to mental health treatment and only 0.4% were associated with medical costs of suicide (i.e., attempts and completions). The total costs listed above excluded cost of lives lost to suicide (i.e., statistical value of life) because of the rare and uncertain costs directly associated to PTSD and MDD (Eibner et al., 2008). If projected suicide mortality was included in the model, the total costs for PTSD alone estimated to reach $1.2 billion and separately, $2.02 billion for comorbid PTSD and MDD. Several limitations of this model include underestimating the expenses of costs associated with homelessness, domestic violence, family strain, and substance

abuse. Additionally, these estimates were limited to a two-year timeframe, which excludes costs stemming from chronic cases and further psychological and physical turmoil experienced from redeployment (Eibner et al., 2008). Since the introduction of PTSD in 1980, it has been considered one of the primary mental health concerns among U.S. military service members returning from operations overseas (3rd ed.; *DSM-III*; APA, 1980). However, PTSD is a specific disorder and not a catch-all phrase for explaining the mental and physical consequences following stress reaction to a warzone (Litz, 2014).

The majority of research published to date follows the conceptualization of PTSD as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; APA, 2000). Traumatic events may involve exposure to actual or threatened death, serious injury, or a threat to self or others physical integrity (Criterion A1). Specifically, these traumatic events may include violent physical or sexual assaults, childhood neglect, experiencing natural disasters, or severe motor vehicle accidents (APA, 2000). Furthermore, these events can be experienced personally, witnessed happening to another person, or learned about occurring to a family member or close friend. The response to the trauma must involve feelings of fear, helplessness, or horror (Criterion A2). The primary symptoms of PTSD consist of three main clusters. Persistent *re-experiencing* of the traumatic event, which includes distressing nightmares, dissociative flashbacks, and physiological reactivity on exposure to internal or external cues associated with the trauma (Criterion B). *Avoidance* of trauma-related stimuli such as avoidance of conversations, places, activities, or people associated with the traumatic event, and *numbing* responsiveness, which includes detachment from others and restricted range of affect (Criterion C). Finally, persistent *symptoms of increased arousal* that was not present before the trauma as indicated by exaggerated startle response, difficulty falling asleep, irritability, or outbursts of

anger (Criterion D). Specifically, an individual must experience a minimum of one Criterion B symptom, three Criterion C symptoms, and two Criterion D symptoms that are directly associated with the trauma in order to meet criteria for PTSD based on the DSM-IV-TR classification (APA, 2000). These symptoms must continue for at least one month (Criterion E) and cause clinically significant distress or impairment in functioning (e.g., interpersonal, occupational; Criterion F). Lastly, a clinician following the DSM-IV-TR criteria can specify either "acute" (duration of symptoms is less than three months), "chronic" (duration of symptoms is three months or more), or "with delayed onset" (onset of symptoms is at least six months following the associated traumatic event).

It is worthy to note that the current definition for PTSD in the DSM-5 (APA, 2013) guidelines has changed since the DSM-IV-TR publication. The major revisions from the DSM-IV-TR to the DSM-5 include removing PTSD from the Anxiety Disorders chapter and reclassifying under the Trauma- and Stressor-Related Disorders chapter. The diagnostic criteria for PTSD included several significant changes. For instance, meeting criteria for a traumatic event (Criterion A1) is no longer sufficient through electronic sources of media such as pictures, television, or movies (unless the exposure is work-related, e.g., details exposed to first responders or police officers). Furthermore, the DSM-IV-TR Criterion A2 (feelings of fear, helplessness, or horror during exposure to trauma) has been eliminated from the DSM-5 because this immediate reaction has not been strongly associated with the onset of PTSD (APA, 2013). Additionally, the symptom criteria for PTSD in the DSM-5 consist of four clusters through splitting the avoidance/numbing cluster (Criterion C; DSM-IV-TR) into two separate categories: *avoidance* and *negative alterations in cognitions and mood*. Several revisions of specific symptoms within each cluster took place in the DSM-5. For instance, *negative alterations in*

*cognitions and mood* expanded to include symptoms such as guilt, shame, or exaggerated negative beliefs about oneself, others, or the world. Furthermore, the *arousal* cluster added additional symptoms such as reckless or self-destructive behavior. The DSM-IV-TR "acute" and "chronic" specifiers are absent in the DSM-5, but the "with delayed expression" specifier remains. In the DSM-5, a "with dissociative symptoms" specifier was added that includes re-experiencing dissociative symptoms (feelings of being detached from one's body or mind, or perceiving one's surroundings as being unreal or distorted) in response to trauma. Separate diagnostic criteria for evaluating children six years old or younger has also been included in the DSM-5 in order to improve classification of developmental differences.

The purpose of reviewing the diagnostic criteria specified by the DSM-IV-TR and the DSM-5 is to highlight the contemporary guidelines outlined for clinicians and researchers and demonstrate awareness of these diagnostic differences. However, this study used the DSM-IV-TR model to determine the presence of PTSD among participants because data from an ongoing project that adheres to DSM-IV-TR criteria was included in this study.

A veteran with combat-related PTSD may avoid simple tasks such as going to the supermarket or driving a vehicle because the environments may trigger reminders of the traumatic event (Schnurr, Lunney, Bovin, & Marx, 2009). In a systematic review, Schnurr and colleagues (2009) found that military personnel of OEF/OIF operations with PTSD had higher rates of homelessness, decreased work productivity, poorer physical functioning, and lower reported marital and life satisfaction compared to other era veterans and OEF/OIF veterans without PTSD. Furthermore, OEF/OIF veterans with subthreshold PTSD were shown to have a three times higher likelihood of endorsing hopelessness and suicidal ideation over similar era veterans without PTSD, but no difference in reported likelihoods compared to veterans meeting

full criteria for PTSD (Jakupcak et al., 2011). Veterans with subthreshold PTSD were, however, significantly less likely to report prior mental health treatment compared to veterans with threshold PTSD (Jakupcak et al., 2011). This study demonstrates the need for improved mental health screening for veterans experiencing any level of PTSD symptoms because the presence of suicidal ideation may be a potential risk that is likely overlooked.

When evaluating veterans with PTSD from previous eras (World War II, Korean War, and Vietnam War), studies have found significantly higher endorsements of poorer physical and mental health, diminished subjective well-being, and higher rates of interpersonal violence in comparison to similar era veterans without PTSD (Magruder et al., 2004; Zatzick et al., 1997). Additionally, Zatzick et al. (1997) reported that a sample of veterans diagnosed with PTSD that served before OEF/OIF conflicts were 3.3-fold more likely to report an inability to perform certain roles such as occupational work, school attendance, or household responsibilities relative to veterans without the disorder (Zatzick et al., 1997). Importantly, this finding by Zatzick et al. was evident after controlling for demographic variables and co-occurring psychiatric or medical disorders. These studies suggest the harmful consequences of PTSD impair broad areas of functioning and extend across multiple U.S. military operations over the course of history.

If a veteran develops a mental or physical injury due to active military service, this individual may be eligible to receive monetary disability compensation from the U.S. Department of Veterans Affairs (VA, 2014b). Even if the related disability presents after service, as long as the disability is service-related, monetary compensation from the VA is available. The recipient of monetary disability compensation from the VA due to illness or injury sustained during military service qualifies as “service-connected.” However, if one receives a discharge under dishonorable conditions, he or she may not be eligible for service-connected

compensation, even if the injury or illness is service-related (VA, 2014c). Qualifying discharges include honorable discharges, general discharges, or under honorable conditions. The scaling of awarded service-connected compensation ranges from the 0% (no disability rating) to 100% (highest disability rating) by increments of 10 percentage points. The VA pays tax-free compensation for service-connected disability monthly, and the amount of compensation is dependent on the extent of the injury and the number of eligible dependents. Some additional benefits that are eligible for service-connected recipients may include vocational rehabilitation and employment services, full coverage of health care costs from Veterans Health Administration medical services, life insurance, grants toward housing, supporting costs of nursing home services, and educational and health insurance benefits to family members (VA, 2014b).

In the fiscal year of 2013, the VA reported the following prevalence rates and costs associated with PTSD (VA, 2014c). PTSD ranked as the third most prevalent service-connected disability of all veterans (tinnitus and hearing loss ranked as number one and two, respectively). Additionally, PTSD ranked as the number one mental health disability of all compensation recipients at 58.47% (MDD ranked second at 11.73%) and number one mental health disability of new compensation recipients. In the fiscal year of 2013, the VA reported paying an estimated annual amount of $3.03 billion exclusively to new recipients of service-connected compensation. The estimated total amount paid annually for service-connected compensation in 2013 fiscal year was $49.15 billion. Mental health ranked as fifth out of the fifteen most prevalent “body system” disabilities of all compensation recipients and tied for the highest average degree of disability at 30%. Additionally, the total amount of new compensation recipients for mental health disability from the fiscal years of 2009 to 2013 steadily rose (53,226 to 100,515 recipients) with a 20%

increase from the fiscal years of 2012 to 2013. These findings demonstrate the significant impact of PTSD and clear rise in mental health service-connected disability payments by the VA system.

Frueh et al. (2003) demonstrated that motivations to seek service-connected compensation might influence combat veterans likelihood to over report their symptoms of psychopathology. Specifically, this study evaluated combat veterans that were seeking compensation from the VA for any type of disability (including PTSD). Combat veterans who were compensation seeking endorsed significantly higher symptom severities for depression, dissociation, and PTSD via self-report in comparison to non-compensation seeking veterans. Additionally, the compensation-seeking veterans displayed elevated symptom profiles on Minnesota Multiphasic Personality Inventory-2 (Greene, 2000) clinical scales, content scales, and "fake-bad" validity scales. Specifically, these validity scales detect exaggerated psychopathology by examining inconsistent item responses and over reporting on symptoms that even those with severe mental illness deny experiencing. However, there was no difference in the rate of diagnosis for PTSD between the compensation seeking and non-compensation seeking groups as measured by the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995; Frueh et al., 2003). Additional studies found exaggerated reporting on indices of psychopathology and similar rates of PTSD diagnosis in comparison to non-seeking veterans during an evaluation for exclusively combat-related PTSD disability compensation as well (Frueh, Gold, & de Arellano, 1997; Frueh, Smith, & Baker, 1996). Individuals that require mental health treatment may over report their symptoms to increase the probability of receiving needed services. However, motivation to seek compensation may undermine the validity of assessments based on interview and self-report methods and likely, misallocate services away from veterans experiencing military-related PTSD.

Given these data, improving assessment through biological measurement may help assign resources more efficiently for combat veterans with PTSD. At this time, biological observations associated with PTSD have been relatively inconsistent (Zoladz & Diamond, 2013), and therefore, should only be used to enhance the clinical picture in addition to self-reports and diagnostic interviews when considering diagnosis or treatment. The detrimental psychological, physical and monetary consequences of PTSD make improvements in screening and early intervention techniques imperative. Biological markers may provide a future interdisciplinary enhancement of the clinical assessment for diagnosing and treating veterans with PTSD.

### 1.2 Autonomic Nervous System Response to Trauma-related Stimuli

One of the earliest conceptualizations of PTSD symptomatology included documentation of unexplained heart palpitations following exposure to the American Civil War called "soldier's heart," (DiMauro, Carter, Folk, & Kashdan, 2014). Individuals with PTSD display reactivity to environmental cues or memories associated with the trauma such as extreme hyperarousal or distressing intrusive thoughts that may lead to avoidance of triggers connected to the traumatic event (Bryant & Nickerson, 2013). These maladaptive reactions may occur in safe environments that host reminders of the traumatic event. For instance, heightened reactivity such as hypervigilance may have been beneficial overseas or during hostile situations; however, these ramped-up responses become troublesome in response to civilian settings (e.g., fireworks during the Fourth of July). Researchers have examined this characteristic under laboratory settings by exposing patients with PTSD to internal or external stimuli related to the traumatic event (e.g., presenting gunfire and helicopter sounds to veterans with combat-related PTSD). This method, known as symptom provocation, introduces individuals to stimuli that arouse psychological symptoms such as heightened physiological responses familiar to PTSD, but in a controlled and

low threatening environment. Researchers have performed symptom provocation paradigms utilizing diverse stimuli such as trauma-related pictures, sounds, odors, and individualized scripts aimed to elicit recollections of the traumatic event (Bremner et al., 1999; Gerardi, Blanchard, & Kolb 1989; Orr & Pitman, 1993; Rauch et al., 1996; Vermetten, Schmahl, Southwick & Bremner, 2007). Recently, researchers have incorporated virtual reality software to present traumatic events by allowing participants to personally navigate virtual environments using an electronic game-console controller (e.g., driving a military Humvee during the event of an improvised explosive device (IED) detonation, or patrolling a market square while encountering enemy gunfire; Webb, Vincent, Jin, & Pollack, 2015). Researchers have found heightened autonomic nervous system responses from veterans with PTSD after exposure to trauma-related stimuli, such as increases in startle response, heart rate, and skin conductance level (Orr, McNally, Rosen, & Shalev, 2004; Pole, 2007). The ANS is responsible for maintaining bodily functions that do not require an individual to consciously control such as regulating heartbeat, skin temperature, and respiration. One can adjust some of their autonomic functions (e.g., rate of breathing) by directing their focus on this behavior; however, it is not a normal requirement for humans to keep these bodily functions in their constant awareness to perform these actions. The relationship between physiological reactivity of the ANS and exposure to traumatic cues has prompted researchers to investigate whether this process has the potential to signify the presence of PTSD.

Pole (2007) performed a meta-analysis that examined whether physiological data could correctly identify patients with and without PTSD based on measurements of autonomic reactivity. In particular, this meta-analysis included a variety of autonomic responses to standardized traumatic cues (e.g., veterans with combat-related PTSD hearing combat sounds)

and idiographic traumatic cues (e.g., individualized script-driven imagery). Based on thirty-nine published studies measuring physiological reactivity for participants with and without PTSD, the standardized trauma conditions correctly identified participants with an average sensitivity of 77% and specificity of 91%, while idiographic trauma paradigms found an average sensitivity of 65% and specificity of 83% (Pole, 2007). Specifically, measurements of autonomic activity in response to standardized traumatic cues detected true cases of PTSD with 77% reliability, while correctly determining veterans without PTSD 91% of the time, overall. These results suggest that in previous investigations of heightened autonomic activity in response to traumatic cues, researchers improved classification using standardized trauma-related stimuli in comparison to personal, idiographic reminders of trauma. In addition, similar results appeared in a recent autonomic study of physiological measures incorporating standardized combat cues in virtual reality environments with 75% of veterans with combat-related PTSD and 88% of veterans without PTSD correctly classified through stepwise discriminant function analysis (Webb et al., 2015). In summary, PTSD is associated with elevated autonomic activity; however, approximately 23% of patients with PTSD do not display heightened autonomic arousal to exposure cues. In contrast, the original scoring method established by Weathers, Ruscio and Keane (1999) using the Clinician-Administered PTSD Scale (CAPS; Weathers, Keane, & Davidson, 2001) found a sensitivity of detecting 91% of individuals with PTSD, which makes autonomic measures less suitable for screening purposes.

### *1.2.1 Detecting Instances of Malingered Autonomic Arousal*

Another consideration when utilizing physiological reactivity is the impact coaching has on the ability of healthy individuals to display autonomic activity as if they had PTSD. For instance, Orr and Pitman (1993) presented combat veterans with and without PTSD with 30-

second scripts composed from their two most personally stressful combat experiences while recording their physiological responses. On the first assessment, this study found that approximately 72% of the veterans with PTSD displayed heightened physiological reactivity, while 100% of the veterans without PTSD did not exhibit elevated responses within the PTSD range. Orr and Pitman administered the same procedure to veterans without PTSD seven weeks later. However, before administering the procedure again, veterans without PTSD were encouraged to respond as if they actually had PTSD. In the second assessment results, 25% of veterans without PTSD (4 out of 16) were able to increase their autonomic responses (e.g., heartrate) into the PTSD range following instructions to simulate the disorder.

Gerardi et al. (1989) conducted a study with a similar design using two assessments to expose military veterans with and without PTSD to combat sounds to determine whether veterans with PTSD could appear as if they did not have PTSD ("fake good") and whether veterans without PTSD could increase their physiological responses to fake PTSD ("fake bad"). Unlike Orr and Pitman (1993), the study by Gerardi et al. included very precise "fake bad" instructions that specifically encouraged veterans without PTSD to increase their heart rate, blood pressure, and muscle tension because they explained this is how a veteran with PTSD would typically respond to combat sounds. The veterans with PTSD were not able to lower their physiological responses on the second run after receiving instructions to "fake good." However, veterans instructed to fake PTSD did not respond statistically different from veterans with PTSD on measures of heart rate, forehead electromyogram (EMG), systolic blood pressure, fingertip temperature, and skin conductance level during exposure to combat sounds. The study found a significant difference between the true and fake groups of PTSD for diastolic blood pressure ($p < .01$) only. The researchers conducted a discriminant function analysis that correctly identified

66.7% of veterans attempting to fake PTSD (6 out of 9). Thus, it would seem that the majority of veterans without PTSD were unable to display PTSD patterns of autonomic physiological responses.

Another important aspect to consider is applying this technique to real-world settings. The physiological devices that were able to distinguish veterans with and without PTSD were inconsistent across autonomic studies. Specifically, measurements of skin conductance and forehead EMG (which is associated with frowning) were the best discriminators in the malingering study by Orr and Pitman (1993). In contrast, Gerardi and colleagues (1989) found no significant differences for skin conductance and forehead EMG after veterans attempted to fake PTSD, but only diastolic blood pressure. In comparison to the meta-analysis by Pole (2007), both of the malingering studies reported no significant differences for measures of heart rate, while Pole found the most robust findings for heart rate and no significant effect sizes for diastolic blood pressure and forehead EMG responses. Although confirming the diagnosis of PTSD through aggregated physiological measurements is promising, the past findings challenge the overall classification accuracy and include added complexity due to inconsistent findings across specific autonomic devices, which ultimately lower its suitability as a consistent indicator of PTSD.

### *1.2.2 Limitations in Utilizing Autonomic Arousal Screening for PTSD*

It is important to note that similar detection rates have been found for identifying coached malingers of PTSD with autonomic measurements and psychological assessments such as the Miller Forensic Assessment of Symptoms Test (M-FAST; Miller, 2001), the Trauma Symptom Inventory (TSI; Briere, 1995) and the Structured Interview of Reported Symptoms (Rogers, 1992; for review, see Taylor, Frueh, & Asmudson, 2007). Using the M-FAST, Guriel et al. (2004)

correctly identified 68% of coached malingers informed on PTSD symptoms and strategies to remain undetected by validity scales, and detected 90% of these same malingers when combining responses with the TSI. Given the high rates of detecting malingering and minimal time consumption (e.g., M-FAST requires 5-10 minutes to administer), self-reports have clinical utility; however, multiple sources of information should always be taken into account when contemplating malingering (e.g., inconsistencies between self-report and behavioral observations; Taylor et al., 2007). Furthermore, these prior studies lacked recorded measurements after repeated practice and real-world incentives (e.g., monetary compensation-seeking or self-motivated efforts to display significant distress for social support), as well as pharmaceuticals that can diminish physiological activity (e.g., benzodiazepines, beta-blockers; Taylor et al., 2007). Thus, even without comparable incentives or systematic practice available in natural contexts, the autonomic measurements demonstrated difficulty in excluding veterans without PTSD and detecting veterans with PTSD. These drawbacks of limited sensitivity and lowered clinical utility in comparison to diagnostic interviews and self-reports requires further support before applying autonomic devices as screeners for PTSD in medical and psychiatric settings.

### *1.2.3 Possible Explanations for Minimal Autonomic Arousal*

Considerable interest in understanding why some individuals with PTSD display minimal physiological reactivity has advanced several hypotheses. For instance, Orr and colleagues (2004) concluded there is insufficient evidence to support unconscious defenses such as repression or symptoms of emotional numbing. Other possibilities, such as distortions in reappraisal of the traumatic event that led to increases in posttraumatic symptoms years later (i.e., delayed expression of PTSD; Roemer, Litz, Orsillo, Ehlich, & Friedman, 1998; Southwick,

Morgan, Nicolau, & Charney, 1997), and the immense symptom heterogeneity surrounding the current diagnostic conceptualization of PTSD may be considered. For instance, Galatzer-Levy and Bryant (2013) calculated the symptom combinations that satisfied DSM clinical criteria for PTSD diagnosis, as follows: 84,645 combinations for the DSM-III-R, 79,794 combinations for DSM-IV-TR and 636,120 combinations for the DSM-5. The current conceptualization of PTSD (i.e., DSM-5) includes varying responses to trauma such as anxiety-related symptoms and negative cognitions (e.g., guilt, or diminished interest in activities), which may extend reasoning to why autonomic measures have found a lack of consistent physiological responsiveness across individuals diagnosed with PTSD. Although autonomic measurements have demonstrated support of heightened response to traumatic cues, this specific line of research has produced studies for over twenty years and included well above 1,000 adults with PTSD (e.g., Pole, 2007). Shifting the focus towards incorporating newer techniques such as measuring neurological responses to trauma-related stimuli may hold greater potential for expanding biological assessment of PTSD.

### 1.3 Functional Near-infrared Spectroscopy

Researchers have been successfully delivering light sources near the infrared light range to study changes of human neural activity for over the last three decades (Jobsis, 1977; Tian et al., 2014). Today, this method of conducting non-invasive measurements of neural activity through optics is fNIRS. Quasi-experimental fNIRS studies have successfully distinguished controls from individuals with several psychopathologies such as schizophrenia (Kubota et al., 2005; Takizawa et al., 2008), PTSD (Matsuo et al., 2003; Tian et al., 2014), MDD, and panic disorder (Ohta et al., 2008). The study by Takizawa and colleagues (2014) examined the ability of fNIRS to provide differential diagnosis across participants performing a brief verbal fluency

task – psychiatric patients with similar depressive symptoms (i.e., MDD, schizophrenia, and bipolar disorder) and healthy volunteers. Takizawa and colleagues concluded fNIRS correctly classified 74.6% of the participants with MDD, 90.0% with schizophrenia, and 76.9% with bipolar disorder. Although the rates of sensitivity for MDD and bipolar disorder are similar to autonomic measurements discussed earlier, the methodology in performing differential diagnosis with this technology is still in its infancy and has the potential for considerable enhancements in the future. The previous success in applying fNIRS technology to neural investigations of psychopathology supports its utilization in examining neural activation of veterans with PTSD.

In 1977, Frans Jobsis described the feasibility of measuring changes in oxygen concentration by applying near-infrared light sources to the human skull (Jobsis, 1977). Oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) contain molecules called *chromophores*, which absorb the ranges of visible and near-infrared light and therefore, allow detection of oxy-Hb and deoxy-Hb through optical methods. Chromophores are the inherent molecules of a component that are responsible for its color due to absorbing light at certain wavelengths and reflecting others, as evident in chlorophyll and hemoglobin (Huang, Chen, Carroll, & Hamblin, 2009; Karu 1999). Although chromophores absorb light in the visible and infrared light ranges, developers of fNIRS selected light closer to the infrared spectrum because its photons penetrate the human skull more effectively than visible light (Ward et al., 2006). Thus, fNIRS incorporates light sources that deliver near infrared waves between ~ 650-950 nanometers (i.e., 'optical window'), which is relatively transparent to overlying biological tissue, but is strongly absorbed by chromophores of oxy-Hb and deoxy-Hb (Ferrari & Quaresima, 2012; Scholkmann et al., 2014). Furthermore, this 'optical window' has been supported through measured absorption coefficients of different chromophores at this spectral

range (Obrig et al., 2000; Taroni, Comelli, Pifferi, Torricelli, & Cubeddu, 2007; Uludag et al., 2004; Van Veen, Sterenborg, Pifferi, Torricelli, & Cubeddu, 2004; Vogel & Venugopalan, 2003; Ward et al., 2006). Specifically, water largely absorbs light above 950 nm, while oxy-Hb and deoxy-Hb absorb light below 650 nm at similar rates. However, between the 650-950 nm window, deoxy-Hb and oxy-Hb have different peak absorption rates (e.g., 760 nm for deoxy-Hb and 920 nm for oxy-Hb; Ward et al., 2006) and therefore, can be distinguished from each other. A few biological substances have higher absorption coefficients in this 'optical window' (e.g., collagen and cytochrome oxidase); however, their low concentrations in comparison to oxy-Hb and deoxy-Hb make their presence negligible (Scholkmann et al., 2014). For these reasons, the 'optical window' finds a suitable spectral range for detecting changes in oxy-Hb and deoxy-Hb. Two fiber-optic probes placed on the scalp called *light sources* (i.e., light emitting diodes) and *photo detectors* guide this spectral range. Sources generate the light and detectors collect the reflected light exiting the tissue. Following modifications established by the Beer-Lambert law, the measured intensity of reflected wavelengths from the respective chromophores calculate the concentrations of oxy-Hb and deoxy-Hb.

We utilized fNIRS imaging to collect neurological data over alternative functional imaging methods such as functional magnetic resonance imaging (fMRI). Both fNIRS and fMRI measure changes in cerebral blood flow (i.e., hemodynamic response) to determine neural activation. fNIRS assesses neural activity by measuring the rate of near-infrared light absorption of oxy-Hb and deoxy-Hb after accounting for light scattering through a biological tissue (Leon-Carrion & Leon-Dominguez, 2012; Scholkmann et al., 2014). Conversely, fMRI examines neural activation based on the blood-oxygenation level dependent (BOLD) signal measured through the different magnetic properties of oxy-Hb and deoxy-Hb using a superconductive magnet (Amaro

& Barker, 2006). fMRI has a significant advantage of capturing subcortical brain regions, while fNIRS has a standard depth of only several centimeters beneath the skull's surface (Tian & Liu, 2014). Despite this limitation, fNIRS methodology provides several benefits in comparison to fMRI when conducting studies that expose individuals with PTSD to traumatic reminders. Some of these advantages are as follows: less susceptibility to motion artifacts, no acoustic noise, and naturalistic body positioning during imaging (Irani, Platek, Bunce, Ruocco, & Chute, 2007). Specifically, fMRI involves an individual trying to stay motionless inside a 60 cm wide by 120 cm long tube while experiencing 120-dB acoustic noise with mechanical vibration (Amaro & Barker, 2006). Alternatively, fNIRS allows individuals to maintain a comfortable body position during testing, which supports neural evaluation in realistic environments that include social or behavioral situations. As an added benefit, fNIRS is a portable device that also includes models with a wireless design (Irani et al., 2007). Conversely, an fMRI magnet typically weighs between 5 to 10 tons and is considerably more expensive, with prices ranging from $1.5 to $7 million depending on strength of the magnetic field (Amaro & Barker, 2006; Irani et al., 2007).

### *1.3.1 Components of Neural Activation*

fNIRS is a noninvasive imaging method that monitors neuronal activity through continuous measurements of oxy-Hb, deoxy-Hb, and total hemoglobin (sum of oxy-Hb and deoxy-Hb changes) using near-infrared light (Jobsis, 1977). The general reasoning of how the measurements of oxy-Hb and deoxy-Hb demonstrate neural activation starts with the production of adenosine tri-phosphate (ATP) in the brain. ATP is an essential molecule for satisfying energy demands of neural activation. One method of forming ATP is through the oxidative metabolism of glucose (Raichle & Mintun, 2006). Consequently, as brain effort increases, so does the consumption of glucose and oxygen to produce ATP. Reserves of oxygen and glucose are locally

available to meet the demands, but in addition, the dilation of local blood vessels channels these molecules through the brain's vascular system. As a result, increases in cerebral blood flow (CBF) and cerebral blood volume travel to the activated brain region (Ferrari & Quaresima, 2012). This mechanism is neurovascular coupling (Buxton, 2012). Specifically, the CBF transports oxygen to the active region via hemoglobin (i.e., oxy-Hb). Once the oxy-Hb arrives to the active brain region, oxygen separates from hemoglobin and breaks down glucose, which in turn, forms ATP (Raichle & Mintun, 2006). Although the separation of oxygen from hemoglobin and the subsequent consumption of oxygen contribute to higher levels of deoxy-Hb, CBF sends an overabundance of oxy-Hb to the activated brain tissue, which washes out concentrations of deoxy-Hb within the region (Buxton, 2012). Additionally, CBF consistently sends oxy-Hb at higher proportions than the cerebral metabolic rate of oxygen consumption (Buxton, 2012; Fox & Raichle, 1986). That is to say, once neural activity initiates, the availability of oxygen significantly increases in comparison to the metabolic consumption of oxygen because of a significant spike in blood flow to the activated region (Raichle & Mintun, 2006).

This discrepancy at the respective brain region for oxygen-rich CBF received relative to the rate of oxygen consumption, has led to two important discoveries. First, this physiological phenomenon frequently creates a net increase in oxy-Hb that occurs approximately four to six seconds following the onset of neural activity, which allows fNIRS measurement of cerebral activation (Scholkmann et al., 2014). Second, the previous chain of events describing CBF and oxygen consumption in response to neuronal activity should not be viewed as taking place in a sequential order, but instead, complicated physiological mechanisms that proceed in a parallel fashion (Attwell & Iadecola, 2002; Buxton, 2012; Raichle & Mintun, 2006). Specifically, both processes of oxygen consumption and CBF respond to neural activity; however, sufficient

reserves of glucose and oxygen are locally available to sustain oxygen consumption, which suggests to researchers that CBF may serve other purposes than responding to metabolic needs. For instance, some researchers believe the increase in CBF may be responsible for temperature or ionic balance regulation during neural activation; however, this relationship still requires further investigation (Buxton, 2012; Raichle & Mintun, 2006). See Figure 1-1 for illustration of neural activation as measured through fNIRS. Taken together, when neural activation of specific brain regions commences, local oxygen and glucose is consumed within milliseconds (i.e., metabolic consumption of oxygen begins). Approximately four to six seconds later, vascular dilation of local blood vessels and increases in CBF and cerebral blood volume reaches the activated region, which subsequently produces influxes of oxy-Hb and concomitant decreases in concentrations of deoxy-Hb.

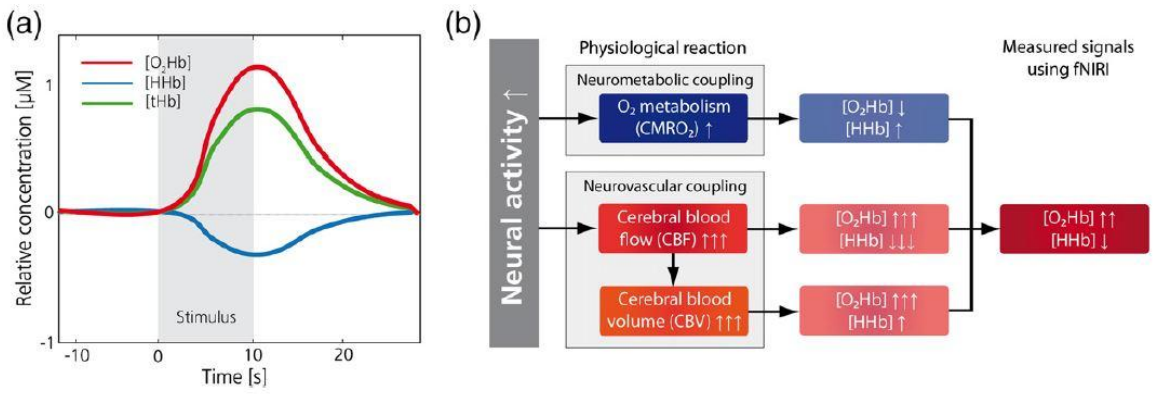



Figure 1-1: Typical evoked changes in cerebral oxygenation and hemodynamics due to an increase in brain activity. Diagram (a) is the neural response measured through fNIRS. Diagram (b) is the metabolic and vascular response during neural activity. *Note*: "fNIRI" is an alternative term for fNIRS. $O_2Hb$ = oxygenated hemoglobin; HHb = deoxygenated hemoglobin; tHb = total hemoglobin; $CMRO_2$= consumption rate of oxygen; µM = change in chromophore concentrations. Adapted from "A Review on Continuous Wave Functional Near-infrared Spectroscopy and Imaging Instrumentation and Methodology," by F. Scholkmann, S. Kleiser, A. J. Metz, R. Zimmermann, J. M. Pavia, U. Wolf, and M. Wolf, 2014, *NeuroImage, 85*, p. 17, Copyright 2014 by Elsevier, Inc.

### *1.3.2 Neural Response to Trauma-related Stimuli using fNIRS*

To our knowledge, only one study has examined a symptom provocation paradigm on individuals with PTSD using fNIRS imaging (Matsuo et al., 2003). Neutral and trauma-related video clips were displayed to two groups of participants present during the Tokyo Subway Sarin Attack in 1995 (participants with PTSD, $n$ = 8; participants without PTSD, $n$ = 26) and 12 healthy volunteers that were not exposed to the traumatic event. In summary, participants exposed to the attack (with or without PTSD) displayed patterns of increased oxy-Hb during the trauma-related video (i.e., video clip showing real news footage from the scene of the Tokyo Subway Sarin Attack in 1995). However, only participants with PTSD displayed significant decreases in deoxy-Hb during the trauma-related clip. These results indicated that individuals with PTSD display an increase in oxy-Hb and a significant decrease of deoxy-Hb in the

prefrontal cerebral regions during the presentation of traumatic images, which is indicative of neuronal activation measured by fNIRS.

### *1.3.3 Meta-analyses of Neural Responses to Trauma-related Stimuli*

The utilization of fNIRS has received less attention until recent years in comparison to other neuroimaging devices such as fMRI and positron emission tomography (PET). As a result, it is necessary to review the current findings of symptom provocation paradigms using alternative neurological devices to provide a comprehensive view. Only a couple of meta-analyses have analyzed the neural activity of individuals with PTSD in response to trauma-related stimuli. A functional neuroimaging meta-analysis conducted by Hayes, Hayes, and Mikedis (2012) on fMRI and PET scan studies examined symptom provocation paradigms comparing participants with PTSD and trauma-exposed controls. They concluded that during symptom provocation, individuals with PTSD exhibited significantly greater activation of the mid- and dorsal anterior cingulate cortex (ACC), and hypo-activation of the ventromedial prefrontal cortex (VMPFC) in comparison to trauma-exposed controls. Taken together, the results of these studies suggest that when individuals with PTSD are exposed to trauma-related cues, they typically exhibit increased activity in regions associated with appraisal (i.e., ACC) and decreased activity in areas supporting regulation of negative emotion such as fear and anxiety (i.e., VMPFC; Etkin, Egner, & Kalisch, 2011). This data suggests that when patients with PTSD typically encounter traumatic reminders, they demonstrate excessive awareness or devote significant cognitive resources on evaluating trauma-related cues, while also having trouble controlling their negative emotions in response to the exposure.

A recent meta-analysis conducted by Sartory et al. (2013) examined the relationship between symptom provocation paradigms and PTSD. Similar to Hayes et al. (2012), both studies

made comparisons to trauma-exposed controls and included PET and fMRI devices. However, Sartory et al. included additional neuroimaging studies and utilized a newer method to calculate regional hyper- and hypoactivation clusters called effect size signed differential mapping, which improves sensitivity and specificity over Hayes et al.'s activation likelihood estimate mapping (for review, see Radua et al., 2012). During presentation of trauma related stimuli, individuals with PTSD displayed hyper-activations of the dorsal ACC; however, in contrast to Hayes and colleagues, they did not find an overall decreased activation of VMPFC relative to trauma-exposed controls. Hypo-activation of the VMPFC is commonly found among individuals with depression (Liotti, Mayberg, McGinnis, Brannan, & Jerabek, 2002), and perhaps, the common comorbidity of depression and PTSD might explain this discrepancy between the meta-analyses (Sartory et al., 2013).

Also in response to traumatic cues, the middle frontal gyrus demonstrated greater activation in participants with PTSD compared to trauma-exposed controls. The middle frontal gyrus is located on the surface of the prefrontal cortex and is well within the range of depth for fNIRS measurements (Tian & Liu, 2014), and thus, this brain region is applicable to our fNIRS investigation. Researchers have found an association between activation of the middle frontal gyrus and empathic responses in young adult civilians (Hynes, Baird, & Grafton, 2006; Masten, Morelli, & Eisenberger, 2011). Since traumatic events often involve witnessing or learning of death or serious injury to close associates, evoking an empathic response would seem plausible when reexperiencing autobiographical memories following exposure to traumatic reminders (Sartory et al., 2013). Trauma-exposed controls also evidenced activation in another prefrontal region (i.e., superior prefrontal cortex) during trauma-related compared to neutral stimuli; however, this activation was not significantly elevated compared to individuals with PTSD.

### *1.3.4 Conclusions from Neurological Studies Presenting Traumatic Cues*

The fNIRS study by Matsuo et al. (2003) suggested that the increased activation in the prefrontal regions might have been a developed effort to inhibit the traumatic stimuli from causing traumatic memories to become reexperienced or problematic, since the majority endorsed currently experiencing non-clinical levels of PTSD symptomatology without any treatment. However, given the salient feature of reexperiencing traumatic memories during the presence of PTSD, the alternative theory postulated by Sartory and colleagues (2013) earlier seems plausible. That is, the significantly increased activation found by Sartory and colleagues in the middle frontal gyrus is associated with empathic responses (Hynes, Baird, & Grafton, 2006; Masten, Morelli, & Eisenberger, 2011). Presenting reminders of a traumatic event may elicit empathic responses because traumatic memories often involve witnessing or learning of death or serious injury to close associates. Although the neural investigations are considerably inconclusive, based on the findings by Matsuo et al. and the meta-analysis by Sartory et al., it is likely an elevation of neural activity in response to traumatic cues will be detected by fNIRS in regions of the prefrontal cortex.

## 1.4 Olfactory Stimuli and PTSD

The act of smelling as a sensory perception has been widely underutilized among researchers examining an individual's physiological reactions to trauma-related stimuli in comparison to other cue forms (e.g., visual, auditory) and therefore, this key sensory process should receive more attention. For instance, the list of scientific studies evaluated by the autonomic and neuroimaging meta-analyses described earlier (Hayes et al., 2012; Pole, 2007; Sartory et al., 2013) did not include olfactory conditions. In the early 1900s, the French writer Marcel Proust described how the smell of a tea-soaked biscuit triggered powerful childhood

memories, and thus, the *Proust phenomenon* describes the ability of smells to evoke autobiographical memories (Chu & Downes, 2000). Herz (2004) examined the *Proust phenomenon* by collecting autobiographical memory ratings for campfire, fresh-cut grass, and popcorn from different cue-forms: verbal, visual, auditory, and olfactory. Immediately following sensory presentation, the researcher(s) asked each participant to think about his or her memory and rate four items. These items were *emotionality*, "how emotional do you feel now as you remember the event," *vividness*, "how vivid or clear is the memory," *evocativeness*, "as you think about the memory, how brought back to the original time and place are you," and *specificity*, "how specific is your memory," (Herz, 2004, p. 219). The odor-evoked autobiographical memories elicited more emotionality ($p < .05$) and evocativeness ($p < .01$), but similar vividness and specificity in comparison to verbal, visual, and auditory cues.

The study by Herz (2004) indicated that olfactory stimuli adds a unique connection between memories and emotional experiences, but should not be misinterpreted as eliciting more accurate memories over other cues (e.g., auditory or visual). 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, Old Spice aftershave) as triggers of military, first responder, and sexual trauma-related PTSD (Kline & Rausch, 1985; Vermetten & Bremner, 2003).

A few neuroimaging studies have examined the relationship between odors associated with the traumatic event and individuals with PTSD. Vermetten et al. (2007) utilized PET scanning to examine neural activations during presentations of a trauma-related odor (diesel fuel) to combat veterans with and without PTSD. They found increased blood flow in the amygdala, insula, medial prefrontal cortex, and ACC, and decreased blood flow in the lateral prefrontal

cortex in participants with PTSD relative to combat controls. The inhalation of diesel fuel was associated with significantly stronger ratings of unpleasantness, higher levels of subjective units of distress, and higher levels of posttraumatic symptoms (e.g., startle, hypervigilance) in combat veterans with PTSD compared to combat controls. Furthermore, researchers found significant neuronal differences for alpha wave activity using an electroencephalogram (EEG) between veterans with and without PTSD in response to the trauma-related odor burnt hair (McCaffrey, Lorig, Pendrey, McCutcheon, & Garrett, 1993). The method of systematically delivering traumatic odors accompanied by measurements of neuronal activation is promising and requires further investigation.

Exposure to war is a unique experience that may impose considerable challenges to physiological and emotional well-being. For instance, combat exposed Reserve and National Guard personnel from the Iraq and Afghanistan wars were significantly more likely to develop new-onset heavy weekly drinking, binge drinking, and alcohol-related problems in comparison to non-deployed service members (Jacobson et al., 2008). MacLean (2010) looked at the longitudinal rates of disability and unemployment across the years of 1968 to 1999 among a sample of civilians ($n$ = 5,124), noncombat exposed veterans ($n$ = 1,297), and combat exposed veterans ($n$ = 546). The findings revealed combat exposed veterans had the highest rates of disability and unemployment in their mid-20s that continued throughout their lifespan, while civilians were ranked second and noncombat veterans had the lowest rates overall. Given the range of responses and coping behaviors to combat exposure, it is essential to analyze the neurological markers of both combat-exposed veterans with and without PTSD in order to distinguish posttraumatic psychopathology from the experience of warfare engagement. Furthermore, performing analyses in comparison to participants without military service can

control for reactions to stimulus presentation from autobiographical memory of combat exposure (Sartory et al., 2013). With this in mind, we included individuals from veteran and civilian communities without PTSD as comparison.

No study was identified that looked at whether the autobiographical event of combat can be distinguished from combat-related PTSD via fNIRS response to trauma-related odors and sounds. The current study aims to examine whether veterans with a current diagnosis of combat-related PTSD display distinct neurological markers in response to a trauma-related odor (i.e., diesel fuel) and trauma-related sound (i.e., explosion). In addition, participants were exposed to other valenced odors and sounds: n-butanol (neutral odor), $H_2S$ or 'rotten egg' (negative odor), a ringing telephone (neutral sound) and an operating dentist drill (negative sound). This study included standardized trauma cues given the improved rates of sensitivity/specificity over idiographic approaches (Pole, 2007). Furthermore, establishing standardized cues will save clinicians valuable time when assessing patients in care settings rather than generating personalized traumatic scripts (Webb et al., 2015). We exposed participants to all traumatic, neutral, and negative odors and sounds. We utilized fNIRS to measure neurological responses, specifically cortical activation through oxy- and deoxy-Hb. During the experiment, participants rated the intensity and pleasantness of the odors and sounds. Specifically, it is hypothesized:

1. Combat veterans with PTSD will display increased activation in the prefrontal cortex during the presentation of trauma-related stimuli relative to civilians and combat veterans without PTSD.
2. Combat veterans with PTSD will rate the trauma-related odor and sound as more unpleasant and intense than both combat veteran and civilian participants without PTSD.

3. Combat veterans without PTSD will show greater neurological activation during presentation of trauma-related stimuli in comparison to civilian controls.

# CHAPTER 2: METHOD

## 2.1 Design

Using a quasi-experimental design, we assessed participants who consisted of three groups: (1) veterans with combat-related PTSD (PTSD+), (2) combat veterans without PTSD (CV), and (3) nonmilitary participants (NM). Participants within the NM group endorsed no current or past history of military service. Using a 3x3 between-subjects design with two separate auditory and olfactory conditions, stimuli were administered in a counterbalanced fashion consisting of randomized stimuli: 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 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 et al., 2007), pervasiveness in recent conflicts (Stuart, Murrary, Ursano, & Wright, 2002), and higher distress ratings among combat veterans with PTSD compared to healthy controls (Cortese, Leslie, & Uhde, 2015).

The auditory/olfactory task paradigm was 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 made subjective ratings on two dimensions: hedonic (pleasant vs. unpleasant) and intensity (weak vs. strong; Appendix A). The intensity and hedonic ratings were similar to German Standard VDI 3882 guidelines (as cited in Frechen, 2000). Intensity was quantified on a 7-point Likert scale (ranges: 0 = *not detectable*; 6 = *intolerable*). Hedonic tone was quantified on a 9-point Likert scale (ranges: +4 = *very pleasant*; -4 = *offensive*).

## 2.2 Participants

Forty-eight (48) males (PTSD+, $n$ = 16; CV, $n$ = 16; NM, $n$ = 16), ages 18 to 56 ($M$ = 32.02 years, $SD$ = 8.47 years), recruited from the community participated in the study. PTSD+ participation was contingent on entering an exposure-based treatment for combat-related PTSD and PTSD needed to be the primary diagnosis. All PTSD+ participants completed the study before receiving treatment. We screened for PTSD using the *Clinician-Administered PTSD Scale* (CAPS; Blake et al., 1995). The CAPS has demonstrated good internal consistency ($\alpha$ = .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 (PTSD+, $\alpha$ = .93; CV, $\alpha$ = .72). We excluded any participants who met criteria for substance abuse 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).

The remaining measures assessed for traumatic brain injury (TBI) history, handedness, and smell acuity: *Ohio State University Traumatic Brain Injury Identification Method* (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 $r = 0.90$; 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). Each participant received $75 in monetary compensation for completing the study.

The demographic survey collected information on age, marital status, race/ethnicity, education, military history, and service connected disability (Appendix A). We utilized non-parametric tests (chi-square, Fisher's Exact test when the expected frequencies were less than five) to analyze the following demographic variables. Overall, the sample was 70.83% Caucasian, 12.50% Hispanic/Latino, 10.42% African American, 4.17% Asian/Pacific Islander, and 2.08% American Indian/Alaskan. Non-parametric tests revealed no significant differences of race across the three groups (Fisher's Exact test, $p = .140$). With regard to marital status across the sample, 43.75% reported married, 39.58% reported single, 8.33% reported divorced, and 8.33% reported separated. There was a significant difference of marital status across the three

groups (Fisher's Exact test, $p = .002$). Compared to the NM group, there were higher rates of marriage and divorce for CV and PTSD+ groups. Additionally, the PTSD+ group reported higher rates of separation than the CV and NM groups, respectively. The education level reported by the sample revealed 45.83% completed some college, 22.92% earned a Master's degree, 16.67% earned a Bachelor's degree, and 14.58% completed high school only. No significant difference for education appeared across groups (Fisher's Exact test, $p = .425$). The branch of service reported across all veteran participants was 59.38% Army, 21.88% Marine Corps, 9.38% Navy, and 9.38% Air Force. The non-parametric test revealed a significant difference for branch of service between groups (Fisher's Exact test, $p = .047$). This finding was likely associated with the substantially higher rate of Marine Corps veterans in the CV group in contrast to the PTSD+ group. However, this finding does not suggest Marine Corps veterans have lower rates of PTSD than other military service branches outside of this study.

All of the participants included in the CV group did not meet current diagnostic criteria for any diagnoses, except for Agoraphobia ($n = 1$). Conversely, participants in the PTSD+ sample met diagnostic criteria for current MDD ($n = 8$), Panic Disorder with Agoraphobia ($n = 2$), and Adjustment Disorder with depressed mood ($n = 1$), which is representative of comorbidity rates among OEF/OIF veterans with PTSD (e.g., Rauch et al., 2015). No participants in the NM group met criteria for any clinical diagnoses.

The OSU TBI-ID, Handedness Questionnaire, and medication log form were not originally administered among PTSD+ and NM groups. We attempted to re-contact 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* = 7/16). All of the CV and PTSD+ participants completed the medication log form. All of the CV and PTSD+ participants, as well as the NM participants successfully re-contacted, screened positive for right handedness. On the OSU TBI-ID assessment, nearly all of the PTSD+ participants completed the interview (*n* = 15/16). However, we are confident that the one missing case did not have any significant 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.

All of the participants screened by the medication log form denied taking any benzodiazepines within at least 24 hours before the assessment. Since 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 .01 to be significant at the $p < .05$ level. See Table 2-1 for the comparisons of age, TBI history, and medication use.

Table 2-1: Frequency (percentage) of Age, Worst TBI History, and Medications across Groups

| | CV | | NM | | PTSD+ | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | Mean | *SD* | | | | | *F* (2, 45) | *Tukey HSD* |
| Age | 31.19 | 5.10 | 27.38 | 8.12 | 37.5 | 8.76 | 7.44** | NM/ PTSD+*** |
| | *N* | % | | | | | *Fisher's Exact* | |
| Worst TBI History | | | | | | | *N* = 38 | |
| No History | 9 | 56.3% | 7 | 100.0% | 1 | 6.7% | <.001*** | |
| Mild TBI w/o LOC | 3 | 7.9% | 0 | 0.0% | 4 | 26.7% | | |
| Mild TBI w/ LOC | 4 | 25.0% | 0 | 0.0% | 10 | 66.7% | | |
| Moderate TBI | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | | |
| Severe TBI | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | | |
| Medications | | | | | | | *N* = 39 | |
| No Medications | 12 | 75.0% | 5 | 71.4% | 3 | 18.8% | .003** | |
| Antidepressants | 2 | 12.5% | 0 | 0.0% | 11 | 68.8% | <.001*** | |
| Anxiolytics | 1 | 6.3% | 1 | 14.3% | 4 | 18.8% | .389 | |
| Antipsychotics and mood stabilizer | 1 | 6.3% | 0 | 0.0% | 7 | 43.8% | .023[a] | |
| Other | 2 | 12.5% | 1 | 14.3% | 15 | 93.8% | <.001*** | |

*Note.* LOC = loss of consciousness. Other = CV participants: albuterol and amino acids; NM participants: amphetamine; PTSD+ participants: antacid, antihistamine, methylphenidate, nonsteroidal anti-inflammatory, melatonin, ibuprofen, thyroid hormone, vitamin D, tryptamine, and proton pump inhibitor.

[a] non-significant following Bonferroni correction for multiple tests.

*$p$ < .05. ** $p$ < .01. *** $p$ < .001.

Within the CV participant group, we verified combat exposure by DD-214 paperwork or official military documentation among active-duty personnel. Fifty percent (50%) of PTSD+ participants and 66.7% of CV participants reported one of their Criterion A events directly

involved an explosion (e.g., IED). Among the CV participants that endorsed a combat-related Criterion A event, the mean CAPS total score was 14.80 (*SD* = 9.81, Range = 1-32), whereas the PTSD+ participants earned a mean CAPS total score of 93.81 (*SD* = 21.00, Range = 53-127).

Measures were administered under supervision of licensed clinical psychologists. Twenty percent of CAPS and MINI screens were randomly selected for review by a blinded staff member to determine inter-rater reliability, which demonstrated a high degree of agreement on the CAPS (total score ICC = .996; PTSD diagnosis $\kappa = 1.00$) and MINI (psychiatric diagnosis $\kappa = 1.00$).

### *2.2.1 Power and Sample Size Calculation*

G*Power software version 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009) was utilized to calculate statistical power for a needed effect size f value of 0.51. This effect size f value was averaged from the significant hemoglobin levels obtained from the respective group mean and standard deviation values of an fNIRS study of auditory symptom provocation in dental phobia (effect size f value = 0.506; Köchel et al., 2011), and an fNRIS investigation of working memory performance for veterans with PTSD (effect size f value = 0.520; Tian et al., 2014). The observed power based on the averaged effect size f value and respective study sample sizes ranged from .94 to .98 when using an alpha level of .05. Using the following specifications mentioned and a power of .96, the total sample size required for three groups is 45 participants. We recruited 48 participants to have an even number complete the counter-balanced design. Therefore, this study acquired 48 participants, which assigned 16 participants per group.

## 2.3 Instruments

### *2.3.1 Neural Measurement*

NIRSport-88 is a multi-channel, mobile fNIRS device, (NIRx Medical Technologies, LLC, 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 (see Figure 2-1). At each data channel, fNIRS captured hemoglobin concentration levels, sampled at 7.8 Hz. 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 EEG data collection. Localization to Broadmann area (BA) is approximate due to individual differences in brain structure and the lack of anatomical MRI brain scans for this study. We used NIRS Acquisition Software (NIRStar; release 2014, NIRx Medical Technologies, LLC, Glen Head, NY, USA) for data collection.

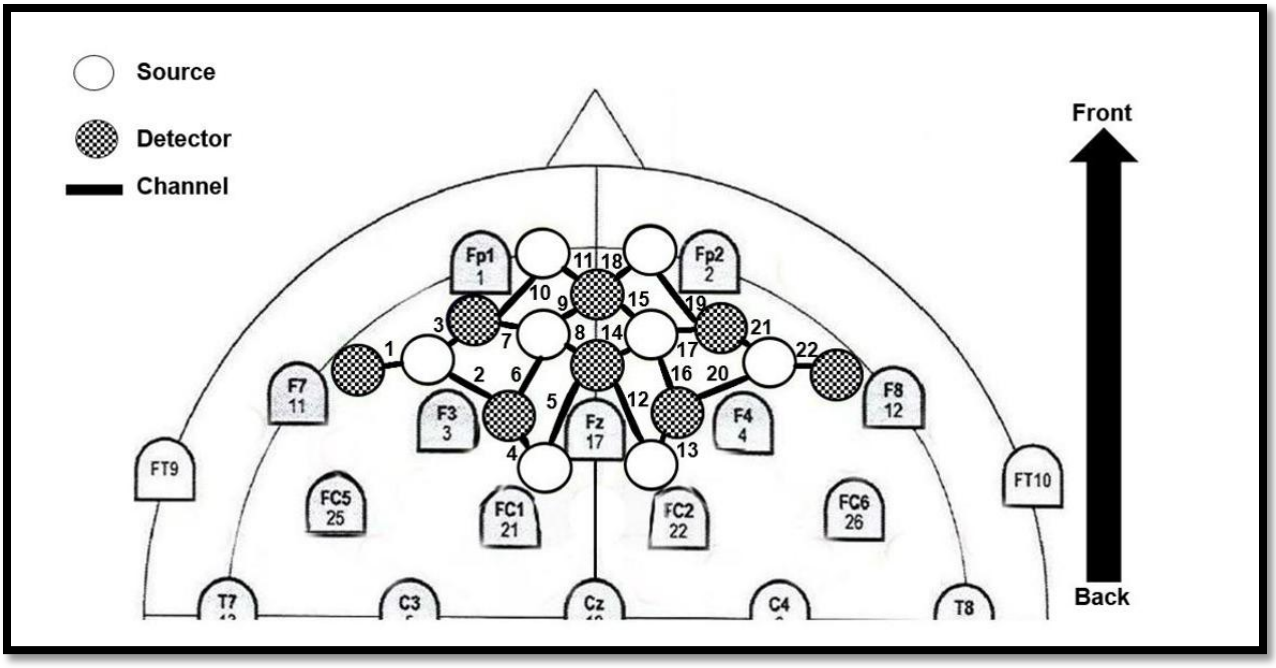



Figure 2-1: fNIRS data collection channels. Channel numbers (1-22) appear adjacent to channel locations. Semicircle markers denote standard EEG 10-20 positions.

### *2.3.2 Auditory and Odor Delivery*

A Windows 8.1. Dell OptiPlex 9020 AIO (Dell Inc.) computer was used to present auditory cues ($M$ = 69.33 dB). An air compressor (California Air Tools, Inc.; CAT – 1610A; 1.0 Hp) pressurized the Scentroid SC300 (IDES Canada, Inc.) mobile olfactometer, which systematically 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.

## 2.4 Procedure

### *2.4.1 Informed Consent*

Once the participant arrived at the University of Central Florida (UCF) clinical psychology laboratories, the researcher measured the participant's head circumference (in cm) at the widest point to select the best-fitting NIRScap size (54 cm, 56 cm, 58 cm, or 60 cm). During the setup of the NIRScap in the experimental room, the researcher conducted consent procedures. The researcher informed the participant that participation is voluntary, discussed the risks and benefits from participating, and explained the limits of confidentiality. Additionally the researcher stated withdrawal from this study was allowed at any time with no penalty, explained the researcher could remove the participant without participant approval if deemed appropriate (e.g., suicidal ideation, failure to follow instructions), and discussed participation in the study was videotaped to ensure the study protocol was conducted correctly. Finally, the researcher provided contact information of the research team, the UCF Institutional Review Board, and the UCF Environment Health & Safety, Risk and Insurance Office in case questions, concerns, or complaints occurred in the future. The participant had the opportunity to fully read the consent form and ask the researcher any questions. After the participant fully understood their participation in the study and provided signature that indicated their permission to take part in this research, the researcher that obtained consent signed the consent form and screened the participant for study eligibility.

### *2.4.2 Screening*

The researcher conducted diagnostic interviews and psychiatric screening in a private laboratory room. Following the psychiatric screening, the eligible participant received the UPSIT

to determine degree of smell acuity. If the participant's sense of smell did not meet study requirements, the researcher notified the participant that he did not qualify for this study and provided the participant with full compensation. However, if the participant displayed impaired smell performance because of a cold or allergies, the researcher offered the participant an opportunity to reschedule. After the researcher reviewed the UPSIT total score and determined whether the participant met study eligibility, the researcher led the participant to the experimental room to complete administration of the auditory and olfactory paradigm.

### *2.4.3 Assessment*

Upon entering the experimental room, the researcher instructed the participant to take a seat in the experimental chair that faced the Dell computer monitor (23 in. screen). The study was conducted in an 18 ft. x 14 ft. experimental room with the participant sitting 64 in. away from the Dell computer monitor. Next, the researcher positioned and secured the NIRScap on the participant; ensuring the Cz electrode centered along both coronal and sagittal midpoints of the head axes. Once the NIRScap was secure, the researcher applied ultrasound gel and inserted source/detector optodes at corresponding sites. Then, the researcher prepared the settings for both auditory and olfactory task conditions on the olfactometer and Dell computer. The order of the tasks was based on whether the participant had an even participant identification number (i.e., olfactory task first) or odd participant identification number (i.e., auditory task first). The researcher programmed the Dell computer to randomize the order of stimuli presentation within each auditory and olfactory condition before administration. The researcher then explained the task instructions to the participant. Following instructions and answering of participant questions, the researcher handed the participant a mouse and a clipboard (in lieu of a mouse pad) for selecting intensity and hedonic ratings during the olfactory and auditory conditions.

The researcher was in the experimental room, but out of participant sight behind a portable wall during the auditory and olfactory conditions. The experimental room had a dimly lit lamp in the far corner of the room throughout the duration of testing. A white fixation crosshair displayed on a black background on the Dell computer monitor during presentation of auditory and olfactory stimuli. Once the participant completed both auditory and olfactory conditions, the researcher removed the NIRScap, provided the participant with directions to the closest bathroom to wash the ultrasound gel from his hair, and personally escorted the participant to the nearest exit.

## 2.5 Behavioral Ratings and fNIRS Analyses

### *2.5.1 Behavioral Ratings Analyses*

Analyses of the behavioral ratings violated parametric assumptions of normality and attempts to normalize the data through various transformations (e.g., log transformations) failed to rectify the significant non-normal distributions. Additionally, the behavioral ratings corresponded to ordinal data and therefore, the hedonic and intensity ratings were analyzed through non-parametric tests (i.e., Kruskal-Wallis test and Friedman's ANOVA). All of the participants were included in the between- and within-subjects analyses described below ($N$ = 48; $n$ = 16 per group). Analyses were conducted using IBM SPSS Statistics version 23.0 (IBM Corp., New York, 2016) with the alpha level set to .05 unless specified otherwise. A Kruskal-Wallis test was performed to determine if between-subject differences existed with the stimuli (negative, neutral, and trauma-related) separately for hedonic and intensity ratings in each auditory and olfactory condition. No violations of the Kruskal-Wallis test occurred in this analysis. A non-parametric Levene's test (i.e., a one-way ANOVA using the ranked absolute

difference scores between groups) revealed non-significant differences ($p > .05$) in the distributions, indicating homogeneity of variance was satisfied for all non-parametric comparisons. Friedman's ANOVA was conducted to determine if any within-subject differences existed among the negative, neutral, and trauma-related stimuli for hedonic and intensity ratings in each auditory and olfactory condition.

### *2.5.2 fNIRS Analyses*

As a first step in preprocessing, 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 oxy-Hb and deoxy-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 et al., 2014). For level 1 (individual participant) analysis, 3 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, as 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). SPM level 2 (group) analysis was carried out on β values estimated during level 1 modeling. The SPM level 1 and 2 sequence constitutes a random effects model analysis (Mumford & Poldrack, 2007). There was no missing fNIRS data among all participants.

A two-way, repeated measures ANOVA (group [PTSD+, CV, and NM] x stimulus [negative, neutral, and trauma-related]) examined oxy-Hb and deoxy-Hb β-values in each auditory and olfactory condition. Two-way repeated measures ANOVAs were performed in SPSS (version 23.0). To control for Type I error, we applied the false discovery rate (FDR) approach to any significant pairwise comparisons (Benjamini & Hochberg, 1995; Pu et al., 2016). Based on the mean β-values, we calculated the between-subjects effect for each significant channel as Cohen's *d* (Cohen, 1988; Lakens, 2013). Additionally, we calculated the within-subjects effect size (i.e., $d_{av}$) to display the amount of oxy-Hb and deoxy-Hb concentration between the experimental (e.g., trauma-related) and rest (baseline) phases (Cumming, 2012). For the within-subjects effect size ($d_{av}$), positive values indicate higher, whereas negative values indicate lower concentrations of the oxy-Hb or deoxy-Hb. Effect sizes were performed using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA).

# CHAPTER 3: RESULTS

## 3.1 Behavioral Ratings Results

### *3.1.1 Between-subjects: Auditory Condition*

The Kruskal-Wallis test revealed significant between-subject differences for the auditory condition. The results showed that trauma-related hedonic ratings were significantly affected by group, $H(2) = 6.40$, $p = .041$. Step-down follow-up analysis revealed that PTSD+ participants had significantly more unpleasant trauma-related ratings (*M* Rank = 17.28) compared to NM and CV participants (*M* Rank = 27.84 and *M* Rank = 28.38, respectively; $p < .05$); however, no significant differences were found between NM and CV participants on hedonic ratings of trauma-related stimuli, $p = .792$. We found no additional significant between-subject differences for the hedonic or intensity behavioral ratings in the auditory condition. See Figure 3-1 for between-subject comparisons of the auditory hedonic ratings.

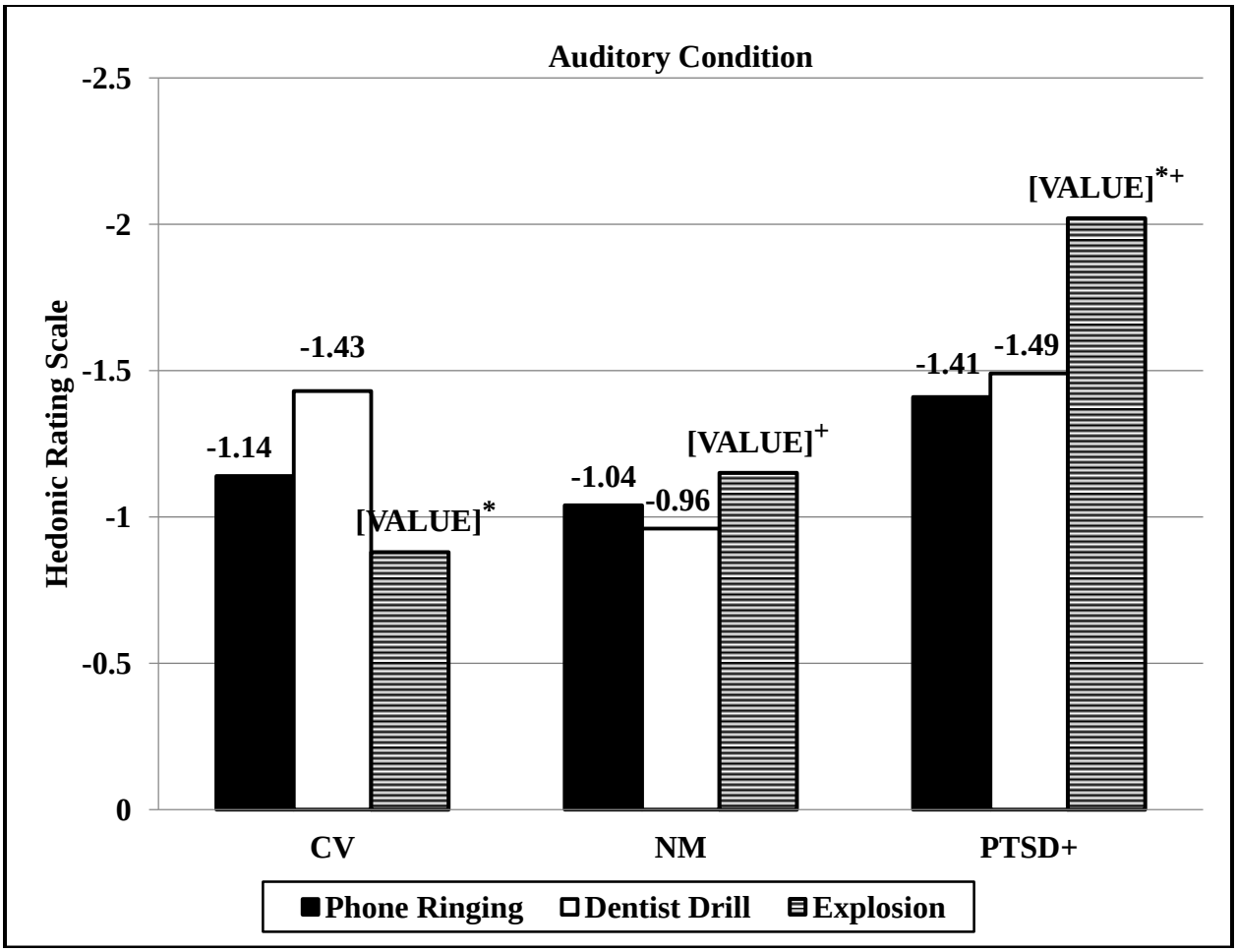



Figure 3-1: Results of the mean auditory hedonic ratings between groups. The PTSD+ participants rated the explosion (trauma-related) sound as significantly more unpleasant than CV and NM participants, $p < .05$. No additional significant differences were found between groups. Hedonic ratings range from -4 (*offensive*) to +4 (*very pleasant*).
$^{*}$ $p < .05$. $^{+}$ $p < .05$.

### *3.1.2 Between-subjects: Olfactory Condition*

The Kruskal-Wallis test revealed significant between-subject differences for the olfactory condition. The results indicated that trauma-related, hedonic ratings were significantly influenced by group, $H(2) = 6.120$, $p = .047$. Step-down follow-up analysis showed that PTSD+ participants had significantly more unpleasant trauma-related ratings (*M* Rank = 18.09) than CV participants (*M* Rank = 30.28; $p < .05$). There were no significant differences between NM participants (*M* Rank = 25.13) and PTSD+ ($p = .168$) or CV ($p = .317$) participants. No further significant

between-subject differences emerged for the hedonic or intensity behavioral ratings in the olfactory condition. See Figure 3-2 for between-subject comparisons of the olfactory hedonic ratings.

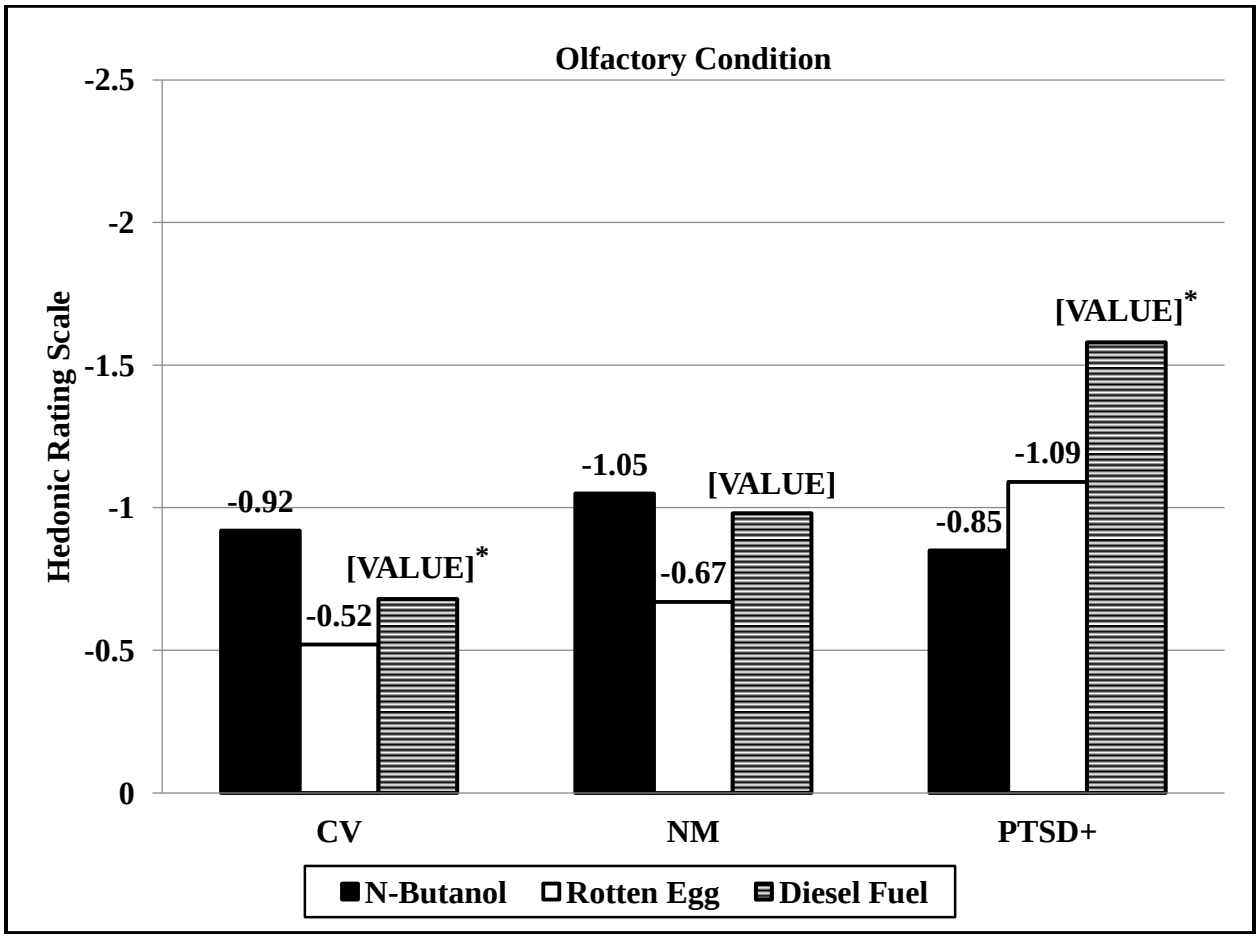



Figure 3-2. Results of the mean olfactory hedonic ratings between groups. The PTSD+ participants rated the diesel fuel (trauma-related) odor as significantly more unpleasant than CV participants, $p < .05$. No additional significant differences were found between groups. Hedonic ratings range from -4 (*offensive*) to +4 (*very pleasant*).
* $p < .05$.

### *3.1.3 Within-subjects: Auditory Condition*

The results showed that auditory stimuli significantly affected the NM participants' intensity ratings, $\chi^2(2) = 9.875$, $p = .007$. Step-down follow-up analysis revealed that the negative intensity ratings (*M* Rank = 1.38) were significantly less intense than the neutral (*M* Rank =

2.44) and trauma-related (*M* Rank = 2.19) intensity ratings. There was no significant difference within the NM group between the intensity ratings of neutral and trauma-related stimuli, $p = .317$. Furthermore, all of the remaining hedonic and intensity within-subject comparisons were non-significant for the auditory condition. See Figure 3-3 for within-subject comparisons of the auditory intensity ratings.

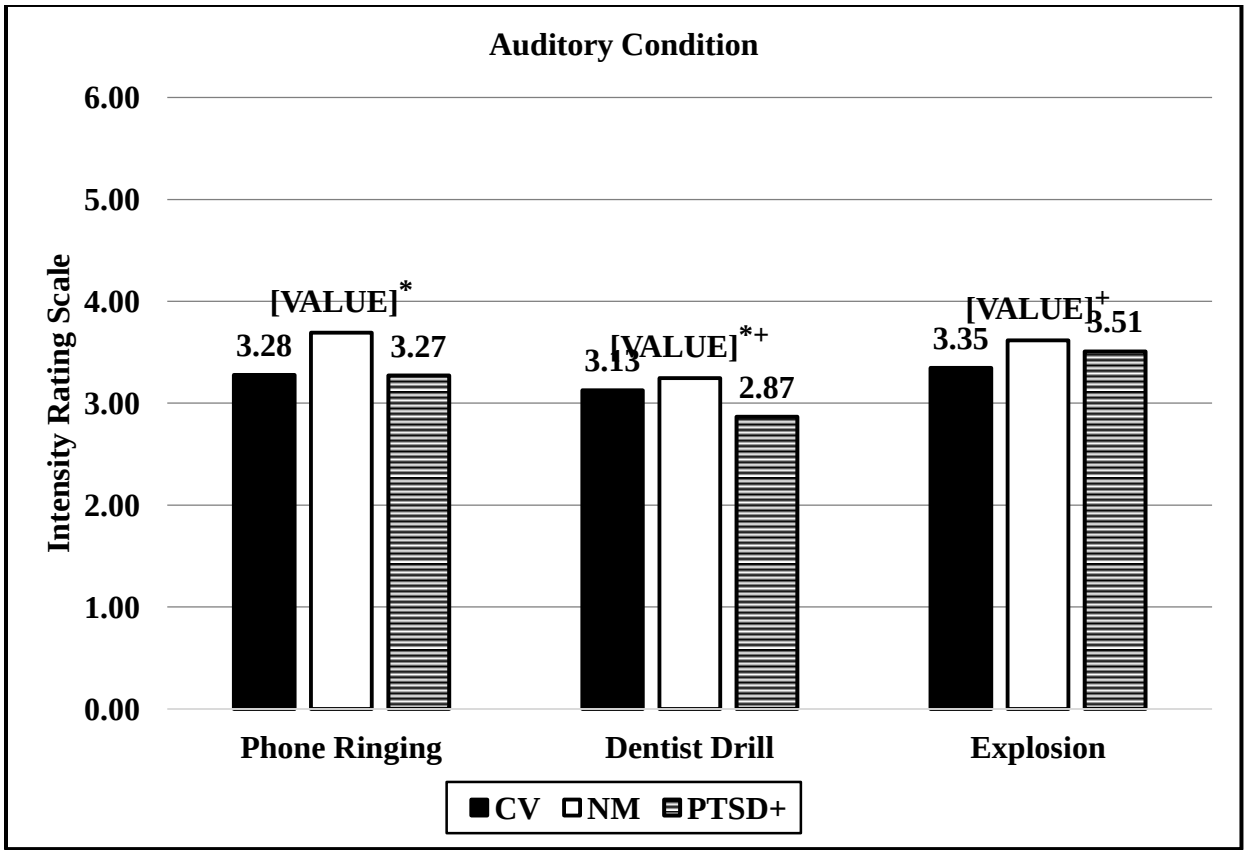



Figure 3-3: Results of the mean auditory intensity ratings within groups. The NM participants rated the dentist drill (negative) sound as significantly less intense than the phone ringing (neutral) and explosion (trauma-related) sounds ($p < .05$). No additional hedonic or intensity significant differences were found within groups. Intensity ratings range from 0 (*not detectable*) to 6 (*intolerable*).
* $p < .05$. + $p < .05$.

### *3.1.4 Within-subjects: Olfactory Condition*

With regard to the within-subject differences for the olfactory condition, the results indicated the olfactory stimuli significantly influenced the NM participants' hedonic ratings,

$\chi^2(2) = 9.68$, $p = .008$. Step-down follow-up analysis revealed that the negative hedonic ratings (*M* Rank = 2.63) were significantly less unpleasant than the neutral (*M* Rank = 1.69) and trauma-related (*M* Rank = 1.69) hedonic ratings. There was no significant difference within the NM group between the neutral and trauma-related hedonic ratings, $p = 1.000$. See Figure 3-4 for within-subjects comparisons of the olfactory hedonic ratings.

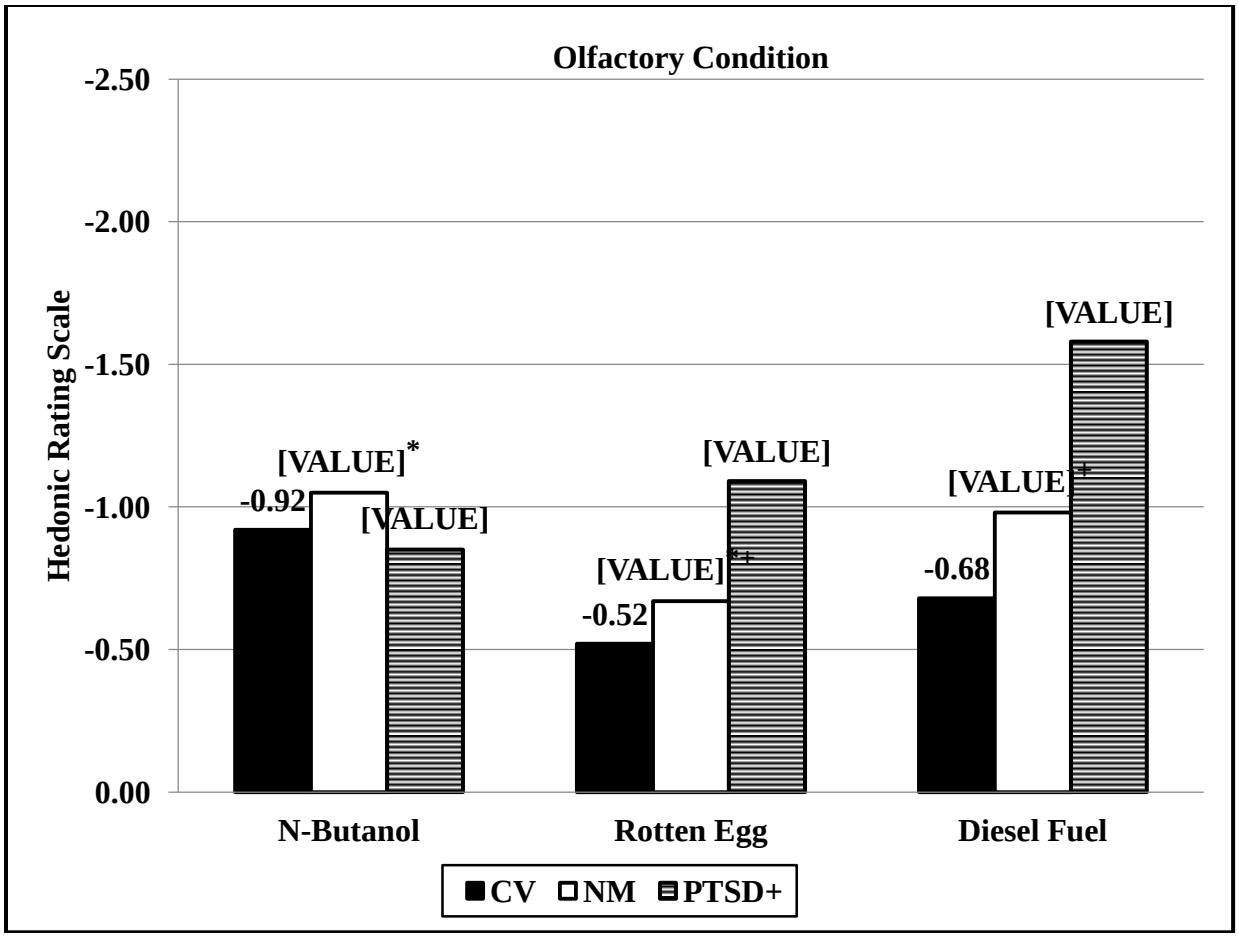



Figure 3-4: Results of the mean olfactory hedonic ratings within groups. The NM participants rated the rotten egg (negative) odor as significantly less unpleasant than the n-butanol (neutral) and diesel fuel (trauma-related) odors ($p < .05$). No additional hedonic significant differences were found within groups. Hedonic ratings range from -4 (*offensive*) to +4 (*very pleasant*). * $p < .05$. + $p < .05$.

The findings revealed the olfactory stimuli significantly affected the PTSD+ participants' intensity ratings, $\chi^2(2) = 6.42$, $p = .040$. Step-down follow-up analysis indicated that the trauma-

related intensity ratings (*M* Rank = 2.41) were significantly more intense than the negative (*M* Rank = 1.53) intensity ratings. There were no significant differences within the PTSD+ group between neutral intensity ratings (*M* Rank = 2.06) and negative ($p = .211$) or trauma-related ($p = .453$) intensity ratings. Additionally, the results showed the olfactory stimuli significantly influenced the NM participants' intensity ratings, $\chi^2(2) = 25.29$, $p < .001$. Step-down follow-up analysis revealed that the negative intensity ratings (*M* Rank = 1.00) were significantly less intense than the neutral (*M* Rank = 2.38) and trauma-related (*M* Rank = 2.63) intensity ratings. There was no significant difference within the NM group between the neutral and trauma-related intensity ratings, $p = .317$. All of the remaining hedonic and intensity within-subject comparisons were non-significant for the olfactory condition. See Figure 3-5 for within-subjects comparisons of the olfactory intensity ratings.

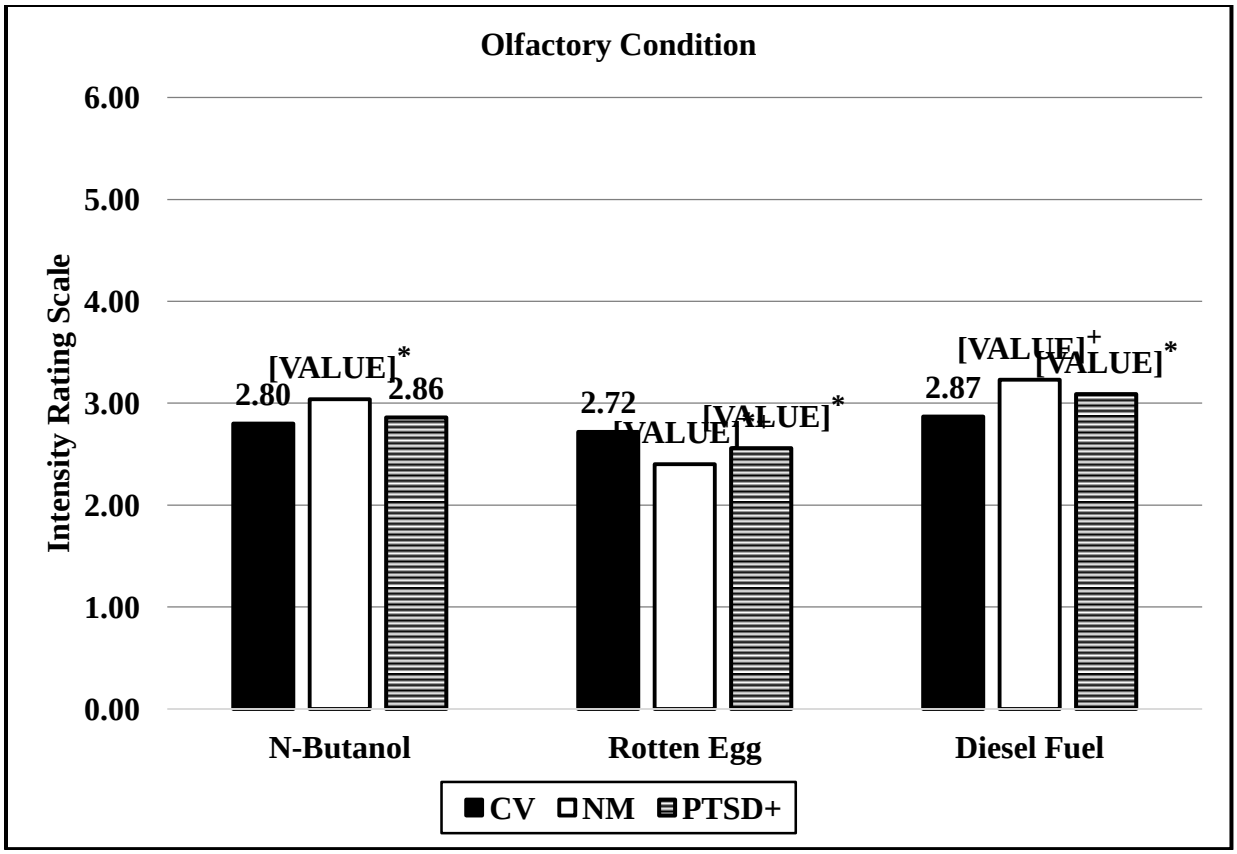


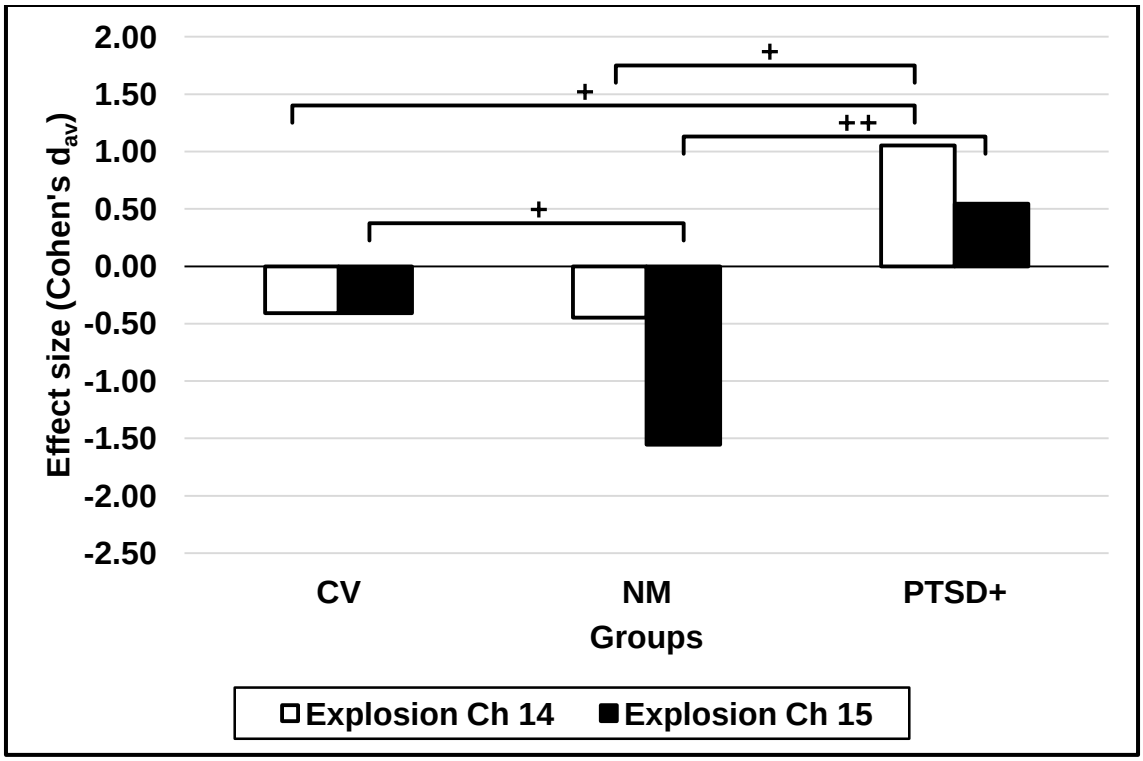

Figure 3-5: Results of the mean olfactory intensity ratings within groups. The NM participants rated the rotten egg (negative) odor as significantly less intense than the n-butanol (neutral) and diesel fuel (trauma-related) odor ($p < .05$). The PTSD+ participants rated the diesel fuel odor as significantly more intense than the rotten egg odor ($p < .05$). No additional intensity significant differences were found within-subjects. Intensity ratings range from 0 (*not detectable*) to 6 (*intolerable*).
$^{*}$ $p < .05$. $^{+}$ $p < .05$.

## 3.2 fNIRS Results

### *3.2.1 Between-subjects: Auditory Condition*

Results of the oxy-Hb auditory condition ANOVA revealed significant between-subject findings for the trauma sound at channels 14 [$F(2,45) = 4.495$, $p = .017$; $\eta_p^2 = .167$] and 15 [$F(2,45) = 7.671$, $p = .001$; $\eta_p^2 = .254$]. Pairwise comparisons indicated significant differences between NM and PTSD+ groups at channels 14 ($p = .006$; $d = 1.03$) and 15 ($p < .001$; $d = 1.30$),

between NM and CV at channel 15 ($p$ = .03; $d$ = 0.84), and between CV and PTSD+ groups at channel 14 ($p$ = .036; $d$ = 0.87). Overall, the PTSD+ group displayed an increase in oxy-Hb at channels 14 and 15; whereas the NM and CV participants exhibited a decrease in oxy-Hb at both of the respective channels (displayed in Figure 3-6). This indicates that only the PTSD+ group showed an increase in neural activation during presentation of the trauma-related sound. After controlling for multiple testing using the FDR, only channel 15 remained significant between NM and PTSD+ groups (i.e., $p \leq .002$). Specifically, the PTSD+ group showed higher concentrations of oxy-Hb than the NM group at channel 15 during presentation of the trauma-related sound. See Figure 3-6 for oxy-Hb SPM images between groups during the trauma-related sound.



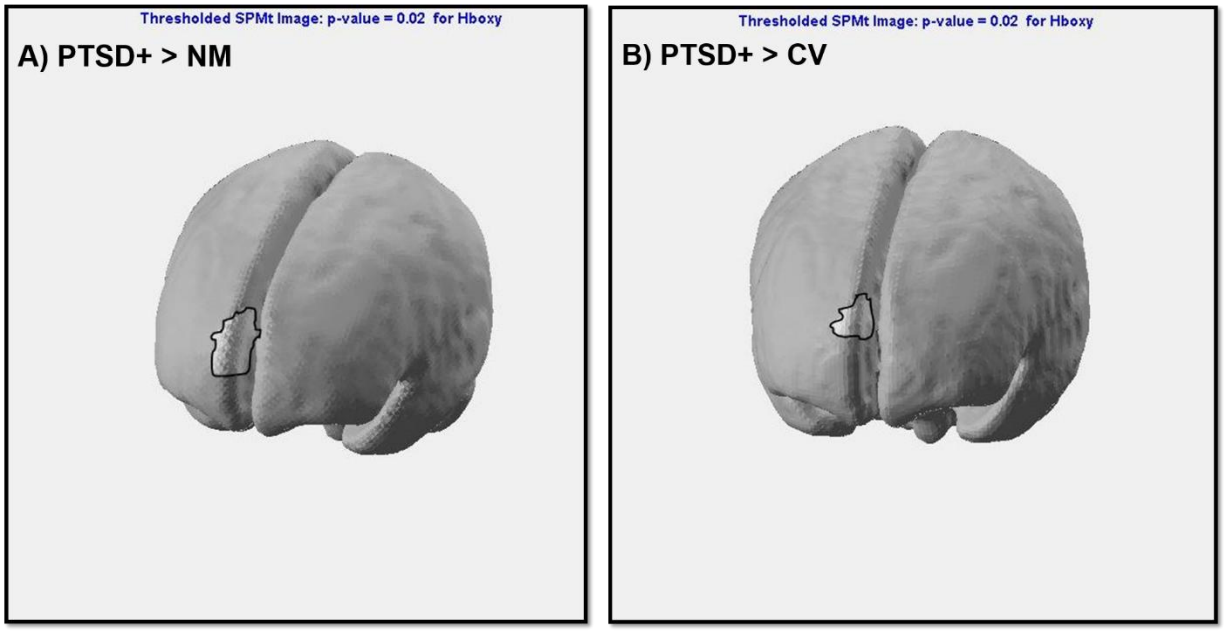




Figure 3-6: Results of oxy-Hb concentrations during presentation of the explosion (trauma-related) sound at channels 14 and 15. SPM images of oxy-Hb concentrations between PTSD+ and NM (image A) and CV (image B) participants during exposure to the explosion sound, which corresponded to channels 14 and 15 (i.e., right superior/medial prefrontal cortex, BA 9/10).
$^{+}$ $p < .05$. $^{++}$ $p \leq .002$ (FDR).

Additionally, results of deoxy-Hb ANOVA for the auditory condition revealed a between-subject significant difference for the neutral sound at channel 10 [$F(2,45) = 4.637$, $p = .015$; $\eta_p^2 = .171$], for the negative sound at channel 9 [$F(2,45) = 3.748$, $p = .031$; $\eta_p^2 = .143$], and for the trauma sound at channel 14 [$F(2,45) = 3.251$, $p = .048$; $\eta_p^2 = .126$]. Pairwise comparisons indicated significant differences between CV and PTSD+ groups at channel 10 for the neutral sound ($p = .004$; $d = 0.93$) and between CV and NM groups at channels 9 for the negative sound ($p = .01$; $d = .084$) and 14 for the trauma sound ($p = .014$; $d = 0.99$). Overall, only the CV group produced a decrease in the concentration of deoxy-Hb during the trauma auditory task at channel 14. Furthermore, only the NM group produced increased concentrations of deoxy-Hb during presentation of negative auditory stimuli at channel 9. No channels remained significant after FDR correction. See Figure 3-7 for the effect sizes of deoxy-Hb concentrations in the auditory condition during presentation of the neutral, negative, and trauma-related sounds.

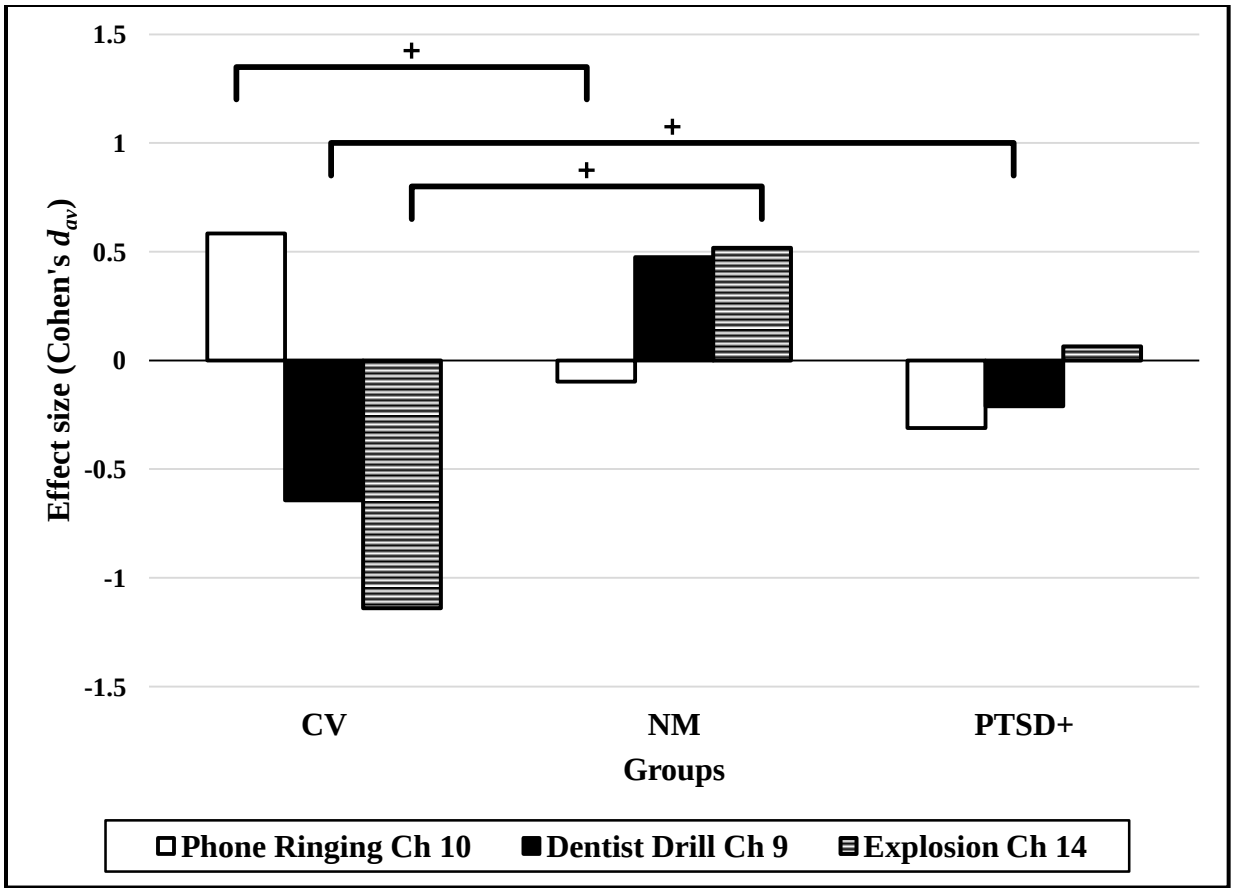



Figure 3-7: Results of deoxy-Hb concentrations during presentation of phone ringing (neutral) sound at channel 10, dentist drill (negative) sound at channel 9, and explosion (trauma-related) sound at channel 14.
$^{+}$ $p < .05$.

### *3.2.2 Between-subjects: Olfactory Condition*

With regard to the oxy-Hb repeated measures ANOVA for the olfactory condition, a between-subjects significant result emerged for the trauma-related [$F(2,45) = 4.773$, $p = .013$; $\eta_p^2 = .175$] and neutral [$F(2,45) = 3.456$, $p = .04$; $\eta_p^2 = .133$] odors at channel 3. Pairwise comparisons indicated significant differences between CV and NM groups at channel 3 for the trauma-related ($p = .005$; $d = 0.92$) and neutral ($p = .019$; $d = 0.74$) odors, as well as significant differences between CV and PTSD+ groups at channel 3 for the trauma-related ($p = .028$, $d = 0.68$) and neutral ($p = .044$; $d = 0.62$) odors. However, no significant differences emerged

between NM and PTSD+ participants. Each group produced an overall decrease in concentration of oxy-Hb during the trauma-related and neutral olfactory tasks at channel 3 (displayed in Figure 3-8). This indicated an overall decrease in neural activation at this region across all of the groups during presentation of trauma-related and neutral odors at channel 3. However, following correction using FDR, no channels remained significant.

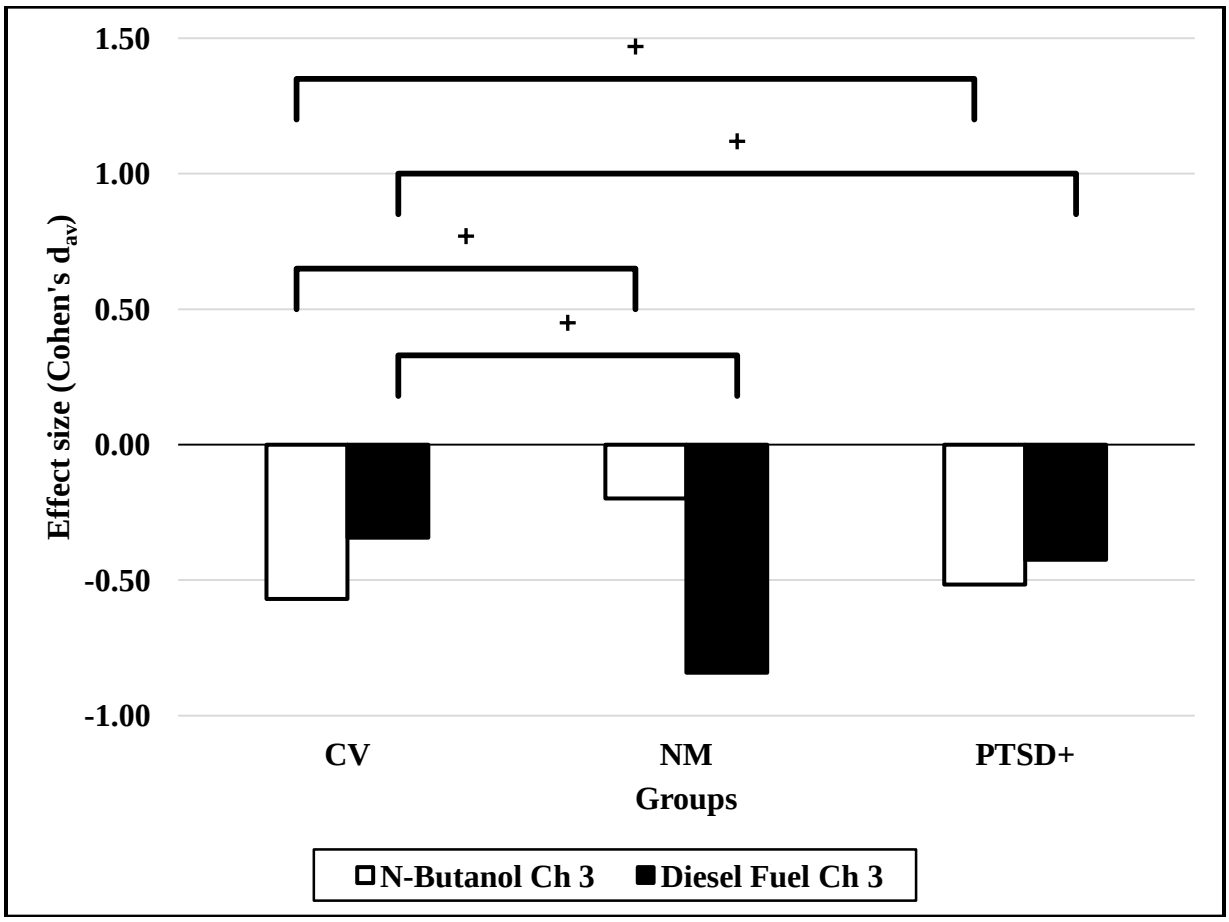



Figure 3-8: Results of oxy-Hb concentrations during presentation of n-butanol (neutral) and diesel fuel (trauma-related) odors at channel 3.
$^{+}$ $p < .05$.

The deoxy-Hb findings for the olfactory condition revealed between-subject significant differences for the trauma odor at channels 3 [$F(2,45) = 3.508$, $p = .039$; $\eta_p^2 = .138$] and 14 [$F(2,45) = 3.888$, $p = .028$; $\eta_p^2 = .150$], as well as the neutral odor at channels 14 [$F(2,45) =$

3.674, $p$ = .033; $\eta_p^2$ = .143] and 15 [$F$(2,45) = 3.311, $p$ = .046; $\eta_p^2$ = .131). Pairwise comparisons showed significant differences between CV and PTSD+ participants for the trauma odor at channel 14 ($p$ = .009; $d$ = 0.77) and the neutral odor at channels 14 ($p$ = .012; $d$ = 0.73) and 15 ($p$ = .034; $d$ = 0.68); whereas CV and NM participants displayed significant differences for the trauma odor at channel 3 ($p$ = .015; $d$ = 0.84) and the neutral odor at channel 15 ($p$ = .029; $d$ = 0.73). Nonetheless, no channel remained significant after performing FDR correction. See Figure 3-9 for the effect sizes of deoxy-Hb concentrations in the olfactory condition during presentation of neutral and trauma-related odors.

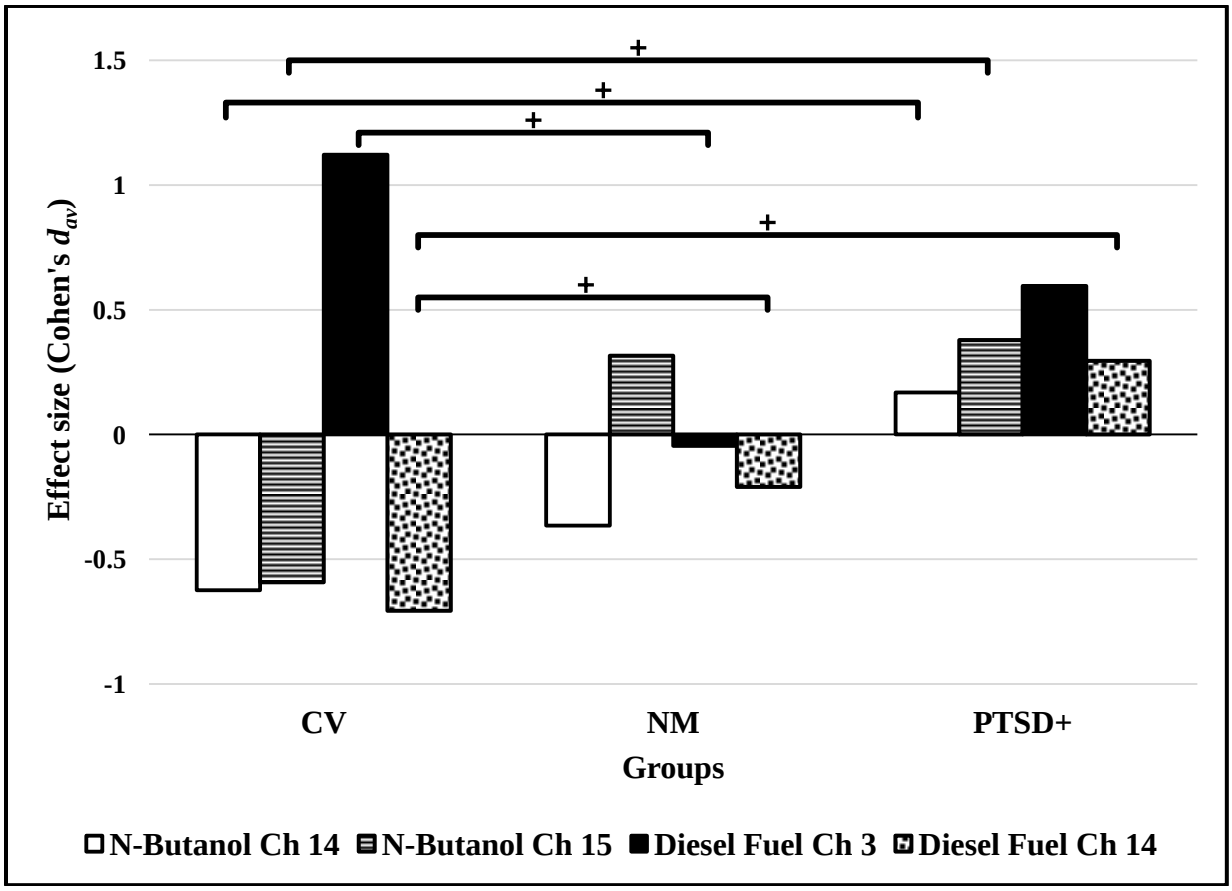



Figure 3-9: Results of deoxy-Hb concentrations during presentation of n-butanol (neutral) odor at channels 14 and 15 and diesel fuel (trauma-related) odor at channels 3 and 14.
$^{+}$ $p$ < .05.

### *3.2.3 Impact of PTSD Severity on fNIRS Activity*

We conducted an exploratory correlation analysis to determine whether a relationship existed between the severity of PTSD symptoms and neural activity. We chose to examine the following conditions and channels based on the significant pairwise findings described above for trauma stimuli between the CV and PTSD+ groups: auditory/oxy-Hb/channel 14, olfactory/oxy-Hb/channel 3 and olfactory/deoxy-Hb/channel 14. Additionally, we chose channel 14 because a significant difference emerged between NM and PTSD+ groups during presentation of the explosion sound and this channel falls alongside channel 15, which remained significant following FDR correction. For severity of PTSD, we examined the CAPS total score ($M$ = 55.55; $SD$ = 7.79) and CAPS subscale scores: re-experiencing ($M$ = 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 test due to bias of non-normality and outliers among fNIRS data and respective CAPS severity scores. We found significant positive correlations between auditory/oxy-Hb/channel 14 and the following PTSD severity scores: CAPS total score [$r$ = .357, $p$ = .048], avoidance subscale score [$r$ = .433, $p$ = .015], and hyperarousal subscale score [$r$ = .455, $p$ = .010]. These findings suggest higher levels of overall PTSD severity, avoidance, and hyperarousal were moderately correlated to increased concentrations of oxy-Hb in the brain region of channel 14 during presentation of trauma-related sounds. See Figure 3-10 for the correlation between PTSD hyperarousal and oxy-Hb concentrations during the trauma-related auditory task.

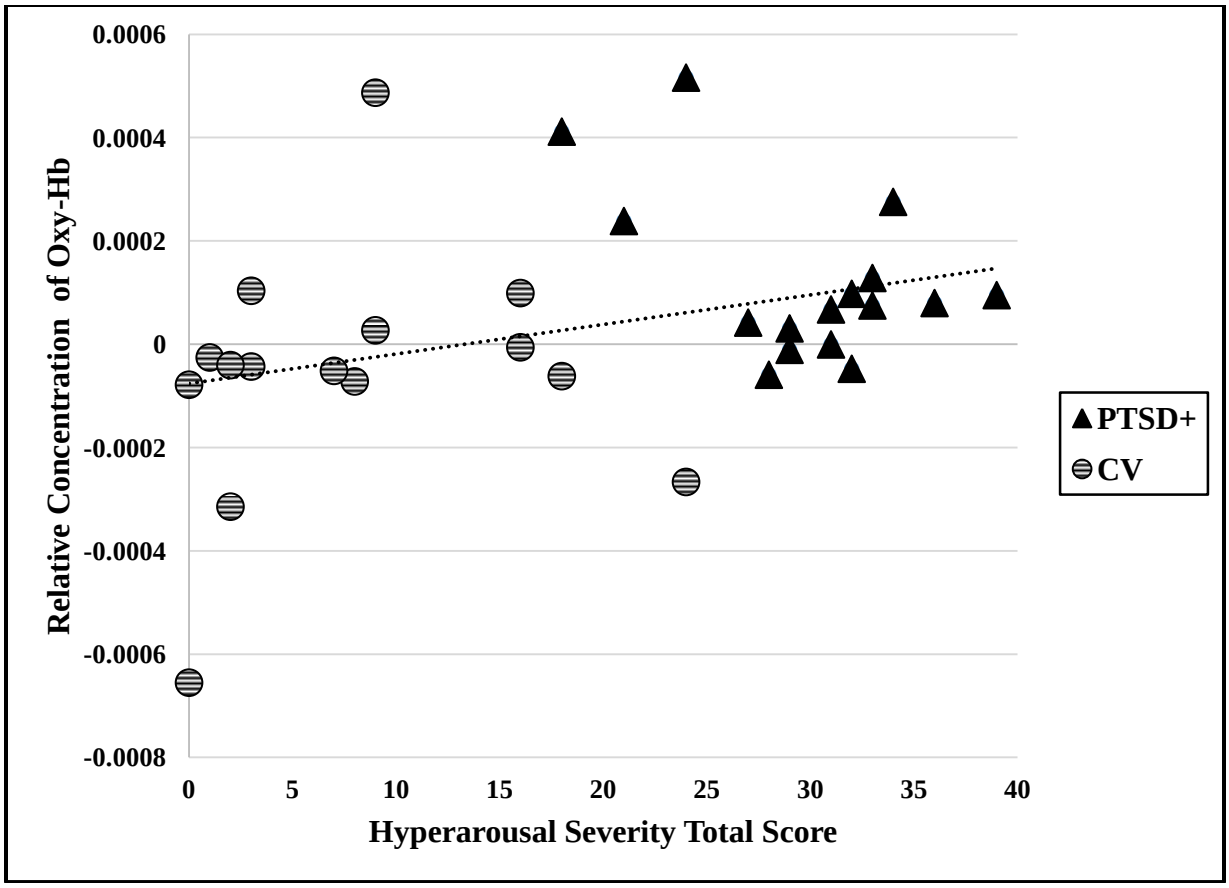



Figure 3-10: Scatterplot of the positive correlation between PTSD hyperarousal severity and oxy-Hb concentration during presentation of the explosion (trauma-related) sound at channel 14. The relative concentration of oxy-Hb is represented by β-values (standardized regression coefficients). We collected the hyperarousal severity total score from the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) for DSM-IV. The hyperarousal severity total score ranges from 0-40.

# CHAPTER 4: DISCUSSION

This is the first investigation examining the neurophysiological response of combat-veterans with PTSD when presented with trauma-related odors and sounds. The results of this study indicate trauma-related auditory cues significantly affect the concentrations of oxy-Hb among veterans with combat-related PTSD compared to individuals without history of combat exposure. Specifically, combat veterans with PTSD displayed a unique neurological response during exposure to trauma-related auditory cues at an area known as the right superior/medial prefrontal cortex (BA 9/10). The outcome of this investigation is consistent with other recent investigations where, increased activation in the right middle frontal gyrus differentiated PTSD participants and trauma-exposed controls during presentation of trauma-related stimuli (Sartory et al. 2013). This meta-analysis supports our findings of higher neural activation in the right superior/medial prefrontal cortex among veterans with combat-related PTSD compared to those with and without combat experience. Furthermore, a recent fNIRS investigation found greater activation of the right compared to the left prefrontal cortex during exposure to negative affective stimuli among non-psychiatric participants (Balconi, Grippa, & Vanutelli, 2015).

Neuroscience investigations have examined the functions of the right superior/medial prefrontal cortex and found associations with evaluating cue familiarity (Schnyer et al., 2004) and emotional detachment (Falquez et al., 2014). 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 superior/medial prefrontal region during presentation

of explosion sounds 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 exercise this technique. Additionally, we found the CAPS avoidance total score demonstrated a significant positive correlation with oxy-Hb concentrations at channel 14 during exposure to the trauma-related sound. Overall, these findings offer a possible neurological explanation linking this region's activation with cognitive processes and possibly extending a biological marker among combat veterans with PTSD.

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 significant cerebral blood flow differences between combat veterans with and without PTSD during diesel smell exposure. Specifically, these authors found increased activation in the right medial prefrontal cortex (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. Nonetheless, it was not determined whether diesel fuel was associated with each combat veteran's traumatic event. For instance, one participant reported after the assessment that he remembered the smells of burning rubber and smoke being associated with his traumatic IED event. Moving forward, we believe a combat-related smell that matches the

traumatic event and is reported by participants as a trigger of PTSD symptoms in everyday experiences will improve the external validity and strengthen the observed effect.

This study failed to show a reliable relationship of the conceptual neural activation model described previously between oxy-Hb and deoxy-Hb at channels 14 or 15 for the PTSD+ group during the explosion sound (Buxton, 2012). That is, an increase in oxy-Hb coupled by a decrease in deoxy-Hb. To our knowledge, Matsuo et al. (2003) conducted the only symptom provocation design using fNIRS between PTSD and trauma-exposed controls (Tokyo, Japan subway terrorist attack). Although Matsuo et al. found an increase of oxy-Hb and concomitant decrease in deoxy-Hb among only the PTSD group, serious caveats apply to the generalizability of this study. First, the sample designated as PTSD included only eight participants – two with current PTSD diagnosis, while the remaining six exhibited subclinical symptoms with a recorded lifetime diagnosis of PTSD related to the terrorist attack. Second, the authors did not report statistical comparisons of neural activation levels between the two trauma-exposed groups: participants with PTSD and participants without PTSD. This publication suggests the possibility of identifying distinct neurological activations through fNIRS methodology; however, the features of this sample and statistical methods utilized encourage further research to support this finding.

We are not surprised by the absence of an inverse relationship between the changes of oxy-Hb and deoxy-Hb following between-subject comparisons because it was also found in several fNIRS investigations among clinical samples (e.g., Helmich et al., 2015; Ohta et al., 2008; Takizawa et al., 2014). In the past, researchers examined the characteristics of oxy-Hb and deoxy-Hb to determine which component suggested changes in neural activation. Strangman, Culver, Thompson, and Boas (2002) found the strongest correlation between the BOLD signal contrast of fMRI and oxy-Hb, while deoxy-Hb was the weakest and total hemoglobin (sum of

oxy-Hb and deoxy-Hb changes) an intermediate. Furthermore, animal studies found the direction of changes for oxy-Hb concentrations and regional cerebral blood flow was in parallel, whereas the direction of changes in deoxy-Hb concentrations was inconsistent (Hoshi, Kobayashi, & Tamura, 2001). Potential reasons for these findings might involve the optical property of oxy-Hb maintaining superior signal-to-noise ratio or the varied physiological functioning of deoxy-Hb in response to blood oxygenation and volume (Hoshi et al., 2001; Strangman et al., 2002). Taken together, we believe oxy-Hb measurements shed light on neural activation and therefore, we focused on oxy-Hb findings to draw conclusions.

### 4.1 Limitations and Future Directions

This study has several limitations. First, fNIRS resolution has limited spatial localization and depth of approximately three cm and therefore, areas supporting the fear and olfactory circuitry such as the amygdala and olfactory bulb were inaccessible (Tian & Liu, 2014). A potential solution may involve conducting investigations using fNIRS and fMRI simultaneously to establish the best neurological picture. Second, as already addressed, this study used standardized trauma-related stimuli that might not resemble each participant's combat-related traumatic event. Post hoc power analyses indicated the significant trauma-related olfactory finding at channel 3 was underpowered by convention (.77), which would require a total sample size of 54 participants to reach power greater than .80 (Cohen, 1992). However, we believe a stronger effect will be obtained by personalized trauma odors over increased sample size. We believed using standardized trauma-related cues across participants was reasonable due to prior effectiveness in research to elicit physiological responses, ease of set up for clinicians to incorporate standardized over ideographic cues in overloaded health care facilities, and preservation of internal validity (e.g., Pole, 2007; Vermetten et. al., 2007; Webb et al. 2015).

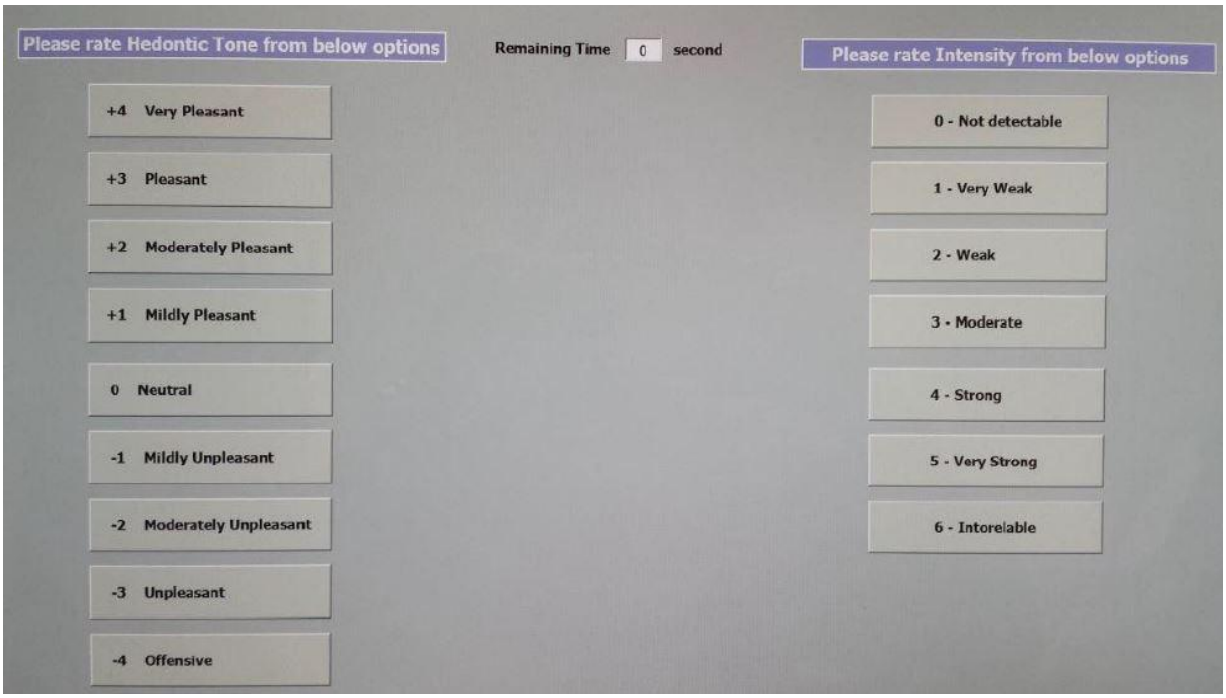
However, this method limits external validity and potentially weakens neural responses and therefore, it is recommended to be replicated using ideographic triggers.

We believe this study has direct applications concerning 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, the VA reported PTSD ranked third among all health disabilities and ranked as the number one mental health disorder among compensation recipients (VA, 2014c). 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 PTSD from other military or civilian traumas (e.g., sexual assault). Furthermore, neurological assessment could benefit clinicians using first-line treatment approaches such as exposure therapy (Goodson et al., 2011). 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, we believe neurological assessment should not replace patient endorsements; however, this scientific method could promote an individualized, comprehensive approach to further assessment and treatment among men and women experiencing combat-related PTSD.

## 4.2 Conclusion

In summary, we found FDR corrected significant differences between the PTSD+ and NM participants for the concentration of oxy-Hb at channel 15 during exposure to the explosion (trauma-related) sound. Moreover, the PTSD+ group revealed considerable positive effect sizes for concentrations of oxy-Hb at channels 14 and 15, whereas the NM and CV groups revealed remarkable negative effect sizes during presentation of the explosion sound. Furthermore, during presentation of the explosion sound, a significant positive correlation was found between PTSD severity and relative concentration of oxy-Hb at channel 14. These channels roughly approximated to the right superior/medial prefrontal cortex and additionally, this approximate region found significant activation among individuals with PTSD compared to trauma-exposed controls in an fMRI meta-analysis of symptom provocation designs (Sartory et al., 2013). Neuroscience investigations linked an association between this brain region with evaluating cue familiarity (Schnyer et al., 2004) and emotional detachment neural networks (Falquez et al., 2014). If replicated, we believe symptom provocation paradigms using fNIRS assessment may extend incremental validity to diagnostic evaluations and further planning and assessment of treatment progress among clinicians treating combat-related PTSD in mental health care facilities.

# APPENDIX A:
INSTRUMENTS


Please rate Hedontic Tone from below options
Remaining Time 0 second
Please rate Intensity from below options
+4 Very Pleasant
+3 Pleasant
+2 Moderately Pleasant
+1 Mildly Pleasant
0 Neutral
-1 Mildly Unpleasant
-2 Moderately Unpleasant
-3 Unpleasant
-4 Offensive
0 - Not detectable
1 - Very Weak
2 - Weak
3 - Moderate
4 - Strong
5 - Very Strong
6 - Intorelable

## Demographic Information

Name: _____ Patient # _____

Address: _____

Phone: _____ DOB: _____ Age: _____

Marital Status (circle one): Married Single Divorced Separated

Race: _____ Sex: _____

Education (circle one): Some High School High School Some College

Bachelors Masters Doctoral

Military History: _____

_____

Branch: _____

Reservist Status: Yes No Unknown MOS: _____

Discharge: Honorable Discharge Dishonorable Discharge _____

War Zone Location(s): _____

Have you had a blast injury? _____ Have you been diagnosed with a TBI? _____

Do you receive service-connected disability? _____

If yes, is it a mental or physical health disability? _____

If yes, what percentage for each disability?

_____% for _____ _____% for _____

_____% for _____ _____% for _____

VA math = _____%

Active Medications: _____

_____

Other Current Treatment: _____

Other Notes: _____

**APPENDIX B:**
INSTITUTIONAL REVIEW BOARD 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-PI: Sandra M. Neer**

Date: **October 08, 2015**

Dear Researcher:

On 10/08/2015, the IRB approved the following minor modification to human participant research until 09/22/2016 inclusive:

| | |
|---|---|
| Type of Review: | IRB Addendum and Modification Request Form |
| Modification Type: | The recruitment flyer has been revised to specify "male" combat veterans and "blood flow" has been changed to "brain responses." |
| Project Title: | Posttraumatic Stress Disorder or Combat Experience? A Functional Near-infrared Spectroscopy Study of Trauma-related Olfactory and Auditory Cues |
| Investigator: | Michael A Gramlich |
| IRB Number: | SBE-15-11605 |
| Funding Agency: | |
| Grant Title: | |
| Research ID: | N/A |

The scientific merit of the research was considered during the IRB review. The Continuing Review Application must be submitted 30days 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 .

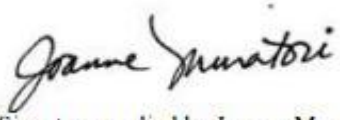
If continuing review approval is not granted before the expiration date of 09/22/2016, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

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 signed and dated 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.

On behalf of Sophia Dziegielewski, Ph.D., L.C.S.W., UCF IRB Chair, this letter is signed by:



Signature applied by Joanne Muratori on 10/08/2015 12:24:39 PM EDT

IRB Manager

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