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Paradoxical olfactory function in combat veterans: The role of PTSD and odor factors

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Abstract

Stress- and trauma-related disorders, including posttraumatic stress disorder (PTSD), are characterized by an increased sensitivity to threat cues. Given that threat detection is a critical function of olfaction and that combat trauma is commonly associated with burning odors, we sought a better understanding of general olfactory function as well as response to specific trauma-related (i.e. burning) odors in combat-related PTSD. Trauma-exposed combat veterans with ($N=22$) and without ($N=25$) PTSD were assessed for general and specific odor sensitivities using a variety of tools. Both groups had similar general odor detection thresholds. However, the combat veterans with PTSD, compared to combat veterans with comparable trauma exposure, but without PTSD, had increased ratings of odor intensity, negative valence, and odor-triggered PTSD symptoms, along with a blunted heart rate in response to burning rubber odor. These findings are discussed within the context of healthy versus pathological changes in olfactory processing that occur over time after psychological trauma.

Keywords

PTSD; odor threat; combat veterans; Olfaction; Psychophysiology

Olfaction serves diverse roles in humans, from eating behavior (Beauchamp & Mennella, 2009; Yeomans, 2006) to social communication and bonding (Stevenson, 2010). Yet one critical function relates to threat detection. Whether alarming us of potentially harmful food, a nearby fire, chemical spill, or gas leak, proper smell functioning, as well as learning which odors signify real danger, is critical to survival. A growing literature suggests that humans demonstrate augmented odor detection and sympathetic arousal (e.g. increased heart rate (HR) and skin conductance level (SCL)) in response to unpleasant and/or fear-related odors (Ahs, Miller, Gordon, & Lundstrom, 2013; Alaoui-Ismaili, Vernet-Maury, Dittmar, Delhomme, & Chanel, 1997; Bensafi et al., 2002a, 2002b), and that odor functioning and

odor-related autonomic responses may be potentiated by acute stress (Krusemark & Li, 2012; Pacharra et al., 2016), high trait anxiety (La Buissonniere-Ariza, Lepore, Kojok, & Frasnelli, 2013), as well as anxiety disorders (Buron, Bulbena, & Bulbena-Cabre, 2015; Pause, Adolph, Prehn-Kristensen, & Ferstl, 2009; Wintermann, Donix, Joraschky, Gerber, & Petrowski, 2013). While the same might be predicted for stress-related disorders like posttraumatic stress disorder (PTSD), available data are limited by the fact that the vast majority of PTSD studies utilize auditory or visual stimuli to provoke symptoms and probe threat-related attentional or autonomic dysfunction (Ashley, Honzel, Larsen, Justus, & Swick, 2013; Bryant & Harvey, 1995; Felmingham, Rennie, Manor, & Bryant, 2011; Morgan, Grillon, Southwick, Davis, & Charney, 1996; Orr, Lasko, Shalev, & Pitman, 1995; Pitman et al., 2001; Pole, 2007; Wahbeh & Oken, 2013).

Yet the olfactory system and odor functioning has important differences from other sensory systems/cues, such that probing this particular system would likely enhance our current understanding of the brain processes involved in stress-related disorders like PTSD. Unlike other sensory systems, the anatomy of the olfactory system (Gottfried, 2006; Kilpatrick & Cahill, 2003; Sevelinges, Gervais, Messaoudi, Granjon, & Mouly, 2004; Stockhorst & Pietrowsky, 2004; Winston, Gottfried, Kilner, & Dolan, 2005; Zald & Pardo, 1997; Zatorre, Jones-Gotman, Evans, & Meyer, 1992) heavily overlaps with the same limbic brain structures and medial temporal lobe circuits that support declarative memory (Brown, Staresina, & Wagner, 2015; Gabrieli, Brewer, & Poldrack, 1998) and emotion processing (Phan, Wager, Taylor, & Liberzon, 2002). Accordingly, odors have the unique ability to trigger some of our oldest and most emotional memories (Chu & Downes, 2002; Nickell & Uhde, 1994; Willander & Larsson, 2006), including memories of traumatic experiences which have been described in a series of case reports (Hinton, Pich, Chhean, Pollack, & Barlow, 2004; Kline & Rausch, 1985; Vermetten & Bremner, 2003). Our survey findings in combat veterans who served in Iraq and Afghanistan (Cortese, Leslie, & Uhde, 2015) are consistent with those prior case reports, revealing that the vast majority, regardless of PTSD status, reported burning odor-related combat experiences. Only the veterans with PTSD, however, endorsed significant burning odor-triggered distress in our survey, which suggests that burning odor sensitivity may not relate to odor-related traumatic experiences per se, but to PTSD.

While these preliminary studies were important first steps in identifying the association between trauma, PTSD, and odor sensitivity, the potential relationships between odor-elicited autonomic responses and specific odor and PTSD factors have yet to be fully explored. For example, just 2 published studies have previously examined physiological responses to odors in PTSD. One measured chemosensory event-related potentials (CSERP) to odors unrelated to trauma in adults exposed to childhood maltreatment (Croy, Schellong, Joraschky, & Hummel, 2010). Although that study reported no group (PTSD versus controls) differences in CSERP, significant relationships between increased PTSD symptom severity subscale scores and faster processing speeds for unpleasant, but not pleasant, odors were revealed. The other published study utilized positron emission tomography (PET) and a trauma-related odor (i.e. diesel) to assess odor-elicited brain responses in Vietnam and Gulf War veterans, revealing a PTSD-related increase in odor-elicited regional cerebral blood flow (rCBF) to limbic and prefrontal brain regions (Vermetten, Schmahl, Southwick, &

Bremner, 2007). While both studies found PTSD-related differences in odor-elicited physiological responses, neither study assessed the relationship between those physiological responses and the psychometric properties of the various odor cues or the degree to which they triggered PTSD symptoms. Ultimately this line of investigation could identify known (and unknown) odor triggers, as well as which individual with PTSD would likely benefit by incorporating specific odors into existing behavioral treatments (e.g. odor-assisted exposure therapy).

Therefore in this laboratory investigation, we sought to assess odor-elicited autonomic reactivity in combat veterans with and without PTSD and determine its relationship to general odor sensitivity, subjective odor ratings, and odor-elicited PTSD symptomatology. Given previous studies showing that odor-elicited HR increased as a function of negative hedonic valence (i.e. unpleasantness) (Alaoui-Ismaili et al., 1997; Bensafi et al., 2002a) and that surveyed combat veterans with PTSD considered burning odors to be unpleasant and elicit significant trauma-related distress (Cortese, Leslie, et al., 2015), we hypothesized increased burning odor-elicited changes in SCL and HR in combat veterans with PTSD compared to healthy veterans. Additionally, we hypothesized that burning odor-elicited physiological changes would positively relate to ratings of odor intensity and negative hedonic valence, as well as ratings of odor-elicited PTSD symptoms, especially in the PTSD group.

Materials and Methods

Participants

Combat veterans with PTSD (CV+PTSD) and without PTSD (CV-PTSD) were recruited from the Ralph H. Johnson VAMC and the greater Charleston community to participate in a larger study investigating general olfactory function and odor-elicited distress using a variety of measurement tools including self-report, psychophysiology, and structural and functional magnetic resonance imaging (MRI). To meet overall eligibility, participants were required to 1) have served in a combat zone in Iraq or Afghanistan; 2) have no self-reported and, if available, medical record-confirmed history of head injury/trauma (e.g., blast exposure, sport injury, etc., given the association between head trauma and olfactory dysfunction); and 3) be psychotropic drug treatment-free and pass a 12-panel urine drug screen (CLIAwaived™, San Diego, CA), so that known and potential unknown drug effects on olfactory and autonomic function could be controlled. Additionally, for the CV+PTSD group, participants were required to meet current (past month) or lifetime DSM-IV primary diagnosis of combat-related PTSD assessed by the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995); for the CV-PTSD group, participants were required to have no history of any DSM-IV disorder including alcohol or other substance-use disorder assessed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Participants provided informed consent prior to the start of study procedures, all of which were approved by the Institutional Review Board at the Medical University of South Carolina.

Procedure

Combat Exposure Scale (CES).—The CES (Keane et al., 1989), a 7-item self-report measure, was used to determine the degree to which various wartime stressors were experienced. Combat veterans rated their exposure to various situations such as the number of times rounds were fired at the enemy or the percentage of soldiers in their unit who were killed, wounded, or missing in action. Items were rated on a 5-point frequency (1 = “no” or “never” to 5 = “more than 50 times”), 5-point duration (1 = “never” to 5 = “more than 6 months”), 4-point frequency (1 = “no” to 4 = “more than 12 times”) or 4-point degree of loss (1 = “no one” to 4 = “more than 50%”) scale. The total CES score, which ranges from 0–41, was calculated by using a sum of weighted scores which was then classified into one of five categories of combat exposure ranging from “light” to “heavy.”

Clinical Olfactory Assessment.—General odor detection/sensitivity was assessed with the Smell Threshold Test™ (STT™, Sensonics, Inc. Haddon Heights, NJ) (Doty, 2009), a series of sniff bottles containing a serial dilution of phenyl ethyl alcohol (PEA), a neutral “rose-like” odor. Sniff bottles were systematically presented until the lowest concentration of PEA that could be reliably detected was determined.

Odor Cues and Measures.—The odor cues (ScentAir™, Charlotte, NC) were selected based upon survey data collected in our laboratory (Cortese, Leslie, et al., 2015) and included burning rubber (BR), a trauma-related “burning” odor cue; lavender (LAV), a relatively pleasant non-trauma-related control odor cue; cigarette smoke (SMK), a non-trauma-related “burning” odor cue; and propylene glycol (PG), which served as the odorless control as well as the base oil for preparing the other odor cues (see Table 1). Similar to previously published methods (Khan et al., 2007), the odor cues were prepared and pilot tested for an average perceived intensity rating of 50 mm on 100 mm visual analog scales (VAS) with anchor points of “not at all” to “extremely”. Using the same 100 mm VAS and anchor points, the following odor ratings were acquired; odor intensity and negative hedonic valence (i.e. unpleasantness), as well as odor-elicited PTSD symptomatology including re-experiencing (i.e., “the odor triggered memories of my trauma”), avoidance/numbing (i.e., “the odor made me feel numb”), and hyperarousal (i.e., “the odor made me feel anxious”). A composite score for odor-elicited PTSD symptoms for each participant was derived as the sum of the individual ratings for odor-elicited re-experiencing, avoidance, and hyperarousal.

Physiological Measures.—Physiological measures were obtained with the MP150 data acquisition system and AcqKnowledge 4.1 software for windows (BIOPAC Systems, Inc., Goleta, CA). HR and SCL were collected in 90-sec epochs according to methods described in-depth previously (Cortese, Uhde, et al., 2015; LaRowe, Saladin, Carpenter, & Upadhyaya, 2007).

Odor Cue Assessment.—The pre-programmed (Superlab 4; Cedrus Corp., San Pedro, CA) odor cue-reactivity study began with a 10-min habituation period (i.e. slideshow of high resolution nature scenes), after which 90-sec baseline HR and SCL were acquired. Next, a study assistant briefly entered the room to deliver the first odor flask and corresponding odor VAS. SCL and HR data acquisition as well as instructions for odor sampling began shortly

after the study assistant exited the room. Odor sampling required participants to remove the cap on the odor flask, pick up and place the odor flask to their nose, inhale 4 times on a 6-s breathing cycle (i.e. 3-s breath in, 3-s breath out, repeated 4 times for a total of 12-s sampling of odor), then replace the capped flask back on the table and breathe normally. Once odor sampling and the 90-sec physiological recording ended, the participants completed the odor VAS, the study assistant briefly re-entered the room to remove all items, and the entire sequence of events was repeated starting with another 10-min habituation period, until all 4 odors were sampled. The delivery sequence for odors was counterbalanced across participants to offset potential order effects. Additional study controls required 1) participants to practice the odor sampling procedures prior to data collection and 2) study staff to monitor (from the audio-/video-linked control room) and confirm proper odor sampling.

Statistical Analyses.—Analyses were conducted using SPSS 23.0. Demographic and clinical characteristics were assessed with Chi-square and Independent t-tests. The laboratory study design provided one within-subjects factor: Odor Type (BR, SMK, LAV, and PG), one between-subjects factor: Diagnosis (CV+PTSD and CV-PTSD), and two key dependent measures: odor-elicited change in HR and SCL. Main effects as well as interactions were determined with repeated measures ANOVA. Two-tailed Pearson's correlation coefficients were utilized to examine potential relationships between clinical, odor, and autonomic measures.

Results

Participant Characteristics

CV+PTSD ($n=22$) were comprised of 18 veterans that met DSM-IV criteria (APA, 1994) for current combat-related PTSD and 4 that met current sub-clinical PTSD (i.e., met criterion A and 2/3 symptom clusters) and met criteria for lifetime PTSD related to their combat experiences. Six CV+PTSD also met diagnostic criteria for secondary depression, 3 had comorbid panic disorder and 1 had comorbid generalized anxiety disorder. CV-PTSD ($n=25$) had no history of any DSM-IV disorder. The number of combat deployments, the degree of combat exposure (Keane et al., 1989), the number of combat-related traumatic experiences and months since the combat-related index trauma (time since trauma, TST), and the percentage of veterans who associated any type of “burning” odor (e.g. burning rubber, diesel exhaust, burning skin, weapon-fire, burning garbage, etc.) with their combat experiences did not differ significantly between CV+PTSD and CV-PTSD (all p s > .1; see Table 2). Combat veteran groups were also well-matched on demographic variables including age, sex, race, education, and employment (all p s > .1), but differed significantly on clinical variables including CAPS-assessed PTSD ($t_{45} = 8.0$, $p < .001$) and 24-item Hamilton Depression Rating Scale (Hamilton, 1960) (HDRS)-assessed depression severity ($t_{43} = 5.6$, $p < .001$) (see Table 2).

General Odor Function

CV+PTSD and CV-PTSD had equivalent odor detection thresholds ($t_{43} = 0.80$, $p > .1$), revealing that combat veterans with and without PTSD demonstrated similar peripheral

olfactory function in response to the neutral “rose-like” odor of PEA. However, both groups performed worse than published age-matched norms (Doty, 2009) (see Table 2).

Odor Ratings

Odor ratings acquired during the odor cue assessment were previously published for 45 of the 47 veterans included in this report (Cortese, McConnell, Froeliger, Leslie, & Uhde, 2015). Our previous report focused on findings from the structural MRI portion of the larger study, describing a PTSD-related decrease in gray matter volume of olfactory cortex that inversely related to specific odor-elicited PTSD symptoms. Updated descriptive statistics for odor ratings in the current (larger) sample are listed in Table 3 and demonstrate generally similar results to those previously reported. Significant Diagnosis by Odor interactions for both odor intensity and negative hedonic valence were revealed. While BR and SMK were rated as more intense by CV+PTSD compared to CV-PTSD, no group differences were found for LAV or PG intensity (Diagnosis X Odor: $F(3,135) = 3.83, p < .05$). Regarding hedonic valence, CV+PTSD, compared to CV-PTSD, were more negative in their ratings for BR and SMK but not PG and LAV (Diagnosis X Odor: $F(3,135) = 4.52, p < .01$). Analysis of a composite score for odor-elicited PTSD symptoms revealed that CV+PTSD endorsed more odor-elicited PTSD symptoms than CV-PTSD (Diagnosis: $F(1,45) = 10.48, p < .01$). While group differences in odor-elicited PTSD symptoms were noted for BR, SMK, and LAV (all $ps < .05$), a Diagnosis X Odor interaction ($F(3,135) = 3.05, p < .05$) and within group comparisons of odor type in CV+PTSD revealed significantly greater symptoms in response to BR and SMK than to LAV and PG, which were not significantly different from each other ($F(3,63) = 10.5, p < .01$).

Physiological Measurements

Odor-elicited HR revealed a main effect of Diagnosis ($F(1,45) = 4.13, p < .05$) and a significant Diagnosis X Odor interaction ($F(3,135) = 2.77, p < .05$). CV+PTSD, compared to CV-PTSD, had an overall reduced odor-elicited HR response, an effect mainly driven by a significantly smaller BR odor-elicited change in HR in CV+PTSD (see Figure 1 and Table 3). No main effect of Odor was found ($p > .1$). Analysis of odor-elicited SCL revealed a main effect of Odor that trended toward significance ($F(3,132) = 2.22, p = .09$). As a whole, combat veterans demonstrated increased SCL in response to BR and SMK compared to PG ($t_{45} = 2.19, p < .05$; $t_{46} = 2.10, p < .05$, respectively). No PTSD-related main or interaction effects were found for SCL ($ps > .1$; see Table 3).

Correlational Analyses

Table 4 lists the Pearson correlation coefficients that were utilized to determine the direction and strength of relationship between clinical variables, odor ratings, and odor-elicited physiological responses. Our initial hypothesis of a positive relationship between BR-odor elicited PTSD symptoms and physiological responses (HR and SCL) was demonstrated only in CV-PTSD, the trauma-exposed but otherwise healthy veterans. Specifically, CV-PTSD who reported the most BR odor-elicited PTSD symptom exhibited the greatest BR odor-elicited increase in HR and SCL ($r = .46, r = .40$, respectively; $ps < .05$). In direct contrast, CV+PTSD showed a trend-level negative relationship between BR odor-elicited PTSD symptoms and HR response ($r = -.41, p < .1$), meaning those who reported the most severe

BR odor-elicited symptoms demonstrated the smallest increases (or in some cases even decreases) in BR odor-elicited HR response. CAPS and HDRS scores were unrelated to BR odor-elicited symptoms and autonomic responses in both groups (all p s > .1).

Relationships between odor measures and time since trauma were also revealed. In CV +PTSD, time since trauma was inversely related to BR odor-elicited HR and SCL ($r = -.58$, $p < .01$; $r = -.45$, $p < .05$, respectively), and positively related to BR odor-elicited PTSD symptoms ($r = .43$, $p < .05$), suggesting that odor-elicited behavioral and physiological responses in PTSD may develop and/or increase in severity over time. In CV-PTSD, time since trauma was negatively related to ratings of BR odor intensity ($r = -.40$, $p < .05$).

Discussion

The present results add to the small, but growing, literature associating changes in odor processing with fear, anxiety, and PTSD in particular. Ratings acquired during the odor challenge test revealed PTSD-related differences in the subjective perception of specific odors. Specifically, odor intensity and negative valence ratings for the burning odors, but not lavender, were significantly increased in CV+PTSD compared to CV-PTSD. In addition, the burning odors were significantly more effective than lavender at eliciting PTSD symptoms in CV+PTSD, yet equally ineffective in CV-PTSD. These results are consistent with the sensitivity to burning odors that post-deployed combat veterans with, but not without, PTSD endorsed through survey (Cortese, Leslie, et al., 2015). They also align with Ahs and colleagues' (2013) findings of a fear-related change in odor sensitivity. In that study of healthy adults, pairing an odor with an aversive stimulus resulted in an odor-specific increase in detection sensitivity, meaning that a lower concentration of odorant was reliably detected post-, compared to pre-, conditioning. While their post-conditioning odor sensitivity effects were transient, returning to pre-conditioning levels by 8 weeks, our results suggest long-lasting burning odor sensitivity in PTSD. In fact, odor-triggered PTSD symptoms were positively related to time since trauma in CV+PTSD, suggesting that unlike general PTSD symptoms, which often reduce in severity over time (Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Perkonig et al., 2005), odor-triggered symptomatology may intensify with time.

Interestingly, an inverse relationship between ratings for burning rubber odor intensity and time since trauma was revealed in CV-PTSD, which is consistent with Ahs and colleagues' (2013) finding of temporary odor sensitivity in healthy adults. We know from our survey data that burning odors (e.g. smoke from weapon-fire and improvised explosive devices (IEDs), etc.) are common to the war theater. Given there were no group differences in the level of combat exposure or percentage who associated burning odors with their combat experiences in the present study, we might assume that burning odors were equally conditioned to traumatic events in both groups of veterans and thus some level of burning odor-related sensitivity, even in healthy combat veterans, was expected. While a longitudinal study design and appropriate comparison group (i.e. never deployed service members) is necessary to confirm whether healthy combat veterans also demonstrate post-trauma odor sensitivity, the present finding of decreased odor intensity ratings as a function of time in

CV-PTSD is consistent with a period of burning odor sensitivity that normalizes in those who do not develop PTSD.

The odor-elicited psychophysiological data in CV+PTSD appeared to question our original hypothesis, which was based upon several lines of evidence including that increased autonomic arousal and exaggerated startle is common in PTSD (Orr et al., 1995; Pole, 2007; Wahbeh & Oken, 2013), and that unpleasant odors typically elicit greater HR increases than pleasant odors (Alaoui-Ismaili et al., 1997; Bensafi et al., 2002a). Those observations would have predicted an increased autonomic response to our trauma cue. However, instead of an expected burning odor-related increase in HR and SCL that correlated with perceived odor properties (i.e. increased intensity and negative valence ratings), CV+PTSD demonstrated a blunted HR response to BR. Interestingly, decreased HR elicited by threatening stimuli may be a component of an alternate strategy for survival, one that possibly aids in the avoidance of predator detection and is characterized by behavioral immobility/freezing (Blanchard & Blanchard, 1969) and HR deceleration or fear bradycardia (Hermans, Henckens, Roelofs, & Fernandez, 2013; Lang et al., 2011). HR deceleration elicited by threatening stimuli may also be a component of a paradoxical process demonstrated in PTSD, whereby individuals report high rates of distress but demonstrate blunted autonomic response to trauma-related cues (Chou, La Marca, Steptoe, & Brewin, 2014; Halligan, Michael, Wilhelm, Clark, & Ehlers, 2006). While some suggest that dissociation plays a prominent role in HR deceleration to trauma cues (Chou et al., 2014; Sack, Cillien, & Hopper, 2012), others suggest that additional factors, including chronicity and trauma load, may influence autonomic responses in PTSD (D'Andrea, Pole, DePierro, Freed, & Wallace, 2013; McTeague et al., 2010). For example, McTeague and colleagues (McTeague et al., 2010) found that blunted startle reflex and SCL were demonstrated only in those that experienced multiple, versus single, traumas, as well as traumas that occurred a longer time in the past. The veterans in the present study experienced their traumatic events on average 5–6 years prior to testing and every veteran in the study reported multiple traumatic exposures, sometimes occurring over multiple combat deployments. Consistent with this notion, CV +PTSD showed inverse relationships between BR odor-elicited HR and SCL and time since trauma, meaning that the greatest autonomic blunting was seen in the veterans who had been experiencing PTSD symptoms the longest.

A differential relationship between odor-triggered PTSD symptoms and odor-elicited autonomic responses was demonstrated for CV+PTSD and CV-PTSD. While HR and SCL increased as a function of increased odor-triggered PTSD symptoms in CV-PTSD, CV +PTSD demonstrated a trending reduction in HR with increasing odor-triggered symptoms. Although it is highly likely that these group differences in odor-elicited PTSD symptoms and autonomic responses developed after olfactory-related trauma and/or the development of PTSD, it is also theoretically possible that baseline differences in odor sensitivity and odor-elicited autonomic responses are pre-morbid (genetic) risk factor for PTSD vulnerability. This will only be determined through longitudinal, pre-trauma and post-trauma, investigation of olfactory function in individuals at high risk for traumatic exposure (e.g. pre-deployed military personnel).

Smell threshold testing revealed no differences in general odor sensitivity between CV +PTSD and CV-PTSD, but uncovered a possible functional impairment in both groups. General odor sensitivity was acquired with the STT™, which provided a standardized assessment tool along with a normative database for detection of PEA, a neutral “rose-like” scent. Although evaluating smell threshold scores against published norms is less rigorous than evaluating against an appropriate comparison group, and should be considered with caution, STT™ scores in both groups of combat veterans were higher (i.e. a higher concentration was needed for reliable detection) than published norms (Doty, 2009). If future testing against a never-deployed control group confirms impaired odor detection, it would be consistent with our previous survey findings that all combat veterans, compared to healthy adults, self-reported less “sensitivity” across many different odors and odor categories, except for a few select odors including burning-related (Cortese, Leslie, et al., 2015). While we acknowledge our finding of impaired odor detection after combat trauma to be preliminary, several theoretical explanations exist if confirmed. First, irreversible damage to the olfactory system could result in a general decreased ability to smell. Yet, physical damage seems inconsistent with increased burning odor sensitivity reported by those with PTSD. A more likely explanation posits a highly-adaptive olfactory system whereby structure and function modulate under situations where/when odor threat detection is critical to survival (Dias & Ressler, 2014; Jones, Choi, Davis, & Ressler, 2008; Morrison, Dias, & Ressler, 2015). For example, pro-survival could require warriors on the battlefield to ignore distracting odor cues while attending to specific odors associated with real and imminent danger. Under these circumstances, physical changes to the olfactory system (e.g. a change in receptor cell number or function) could result in the co-existence of impaired odor detection to a wide range of non-threatening odors (e.g. PEA in the STT™) and enhanced odor detection for specific odor threat cues (e.g. burning). While the current data are consistent with this idea, systematic, longitudinal, smell threshold testing with PEA and a burning odor (e.g. guaiacol), is necessary to determine whether a true dissociation in odor detection exists and how it evolves during and after intensely stressful or traumatic events.

Major strengths of this study include two well-characterized groups of non-medicated veterans with similar combat experiences and no head injuries. However, there are some limitations of this sample, including a cross-sectional design, lack of combat controls, and the use of just one trauma-related odor versus employing odors specific to each participants’ traumatic experiences. Future investigation with individualized trauma odors could demonstrate even greater PTSD-related olfactory effects than found in the present study. Another study limitation relates to the small sample size which precluded a sub-analysis focused on PTSD comorbidity, particularly depression (Brady, Killeen, Brewerton, & Lucerini, 2000). For example, there is a growing literature demonstrating reduced olfactory function in depression (Croy et al., 2014; Pause, Miranda, Goder, Aldenhoff, & Ferstl, 2001). While it is unlikely that depression was a contributing factor in our olfactory results, given the low level of depression in our PTSD group (i.e. HAM-D scores indicated mild depression), the role of depression should be investigated and/or controlled in future PTSD studies.

Conclusion

Many additional questions are generated by the current findings. Our results, however, lay an important and unique foundation for continued work in understanding the role of the olfactory system in stress, trauma, and PTSD. The data suggest increased odor sensitivity to specific odors after combat trauma. While odor sensitivity may normalize with time in healthy veterans, it seems to worsen in those with PTSD. In turn, ineffective strategies that include odor avoidance/numbing and blunted physiological responses may develop, potentially in an effort to cope with intensifying odor sensitivity. Longitudinal testing could help to identify healthy versus unhealthy (PTSD-related) olfactory processing post odor-related trauma, which may ultimately aid in the early identification of PTSD. This testing should include assessments of perceived odor intensity and smell threshold/detection for burning and neutral odors, as well as olfactory neuroimaging, to determine how perceptual changes relate to structural/functional changes in the central olfactory system after traumatic events and with the development of PTSD.

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Public significance statement: Burning odors are commonly associated with combat trauma, yet the role of odors and the olfactory system in PTSD is mostly unknown. Veterans with, but not without, PTSD demonstrated increased fear-related responses to burning rubber odor that included rating it to be more intense and to trigger more PTSD symptoms, as well as eliciting blunted heart rate response. These data add to the literature demonstrating that PTSD is associated with increased sensitivity to threat cues.

Figure 1.

A significant Diagnosis X Odor interaction for odor-elicited HR was revealed [$F(3,135) = 2.77, p < .05$]. Combat veterans with PTSD (CV+PTSD, $n=22$) had reduced BR odor-elicited HR compared to healthy veterans (CV-PTSD, $n=25$) and the other odors. HR measurement in beats per minute (BPM). * = $p < .05$ for planned comparison.

Table 1.

Odor cue abbreviations and descriptions.

Odor Cue	Abbreviation	Description
Burning rubber	BR	Trauma-related “burning”
Lavender	LAV	Non-trauma-related pleasant,
Cigarette smoke	SMK	Non-trauma-related “burning”
Propylene glycol	PG	Odorless control

Table 2.

Demographic and clinical characteristics of study participants

	CV+PTSD (<i>n</i> =22)	CV-PTSD (<i>n</i> =25)	χ^2 or <i>t</i>	<i>p</i>
Sex - <i>n</i> (%) male	21 (95.5)	24 (96.0)	0.01	ns
Race - <i>n</i> (%) minority	8 (36.3)	3 (12.0)	4.20	ns
Employment - <i>n</i> (%) employed	13 (59.1)	15 (60.0)	0.00	ns
Age in years (mean±SD)	30.0±8.1	30.8±7.1	0.38	ns
Education in years (mean±SD)	13.9±1.3	14.6±2.3	1.40	ns
Combat Exposure [*] (mean±SD)	22.2±8.3	20.0±10.0	0.84	ns
Combat Deployments (mean±SD)	2.09±0.9	1.92±0.8	0.68	ns
Combat Trauma (mean±SD)	2.50±0.5	2.72±0.5	1.56	ns
TST in months (mean±SD)	60.6±31.8	70.1±31.3	1.03	ns
Burning odor(s) [§] - <i>n</i> (%) endorsed	19 (86.4)	18 (72.0)	1.44	ns
Odor Detection [#] (mean±SD)	-4.38±1.2~	-4.26±0.9~	0.38	ns
HDRS score (mean±SD)	15.2±9.1	3.7±4.2	5.61	<0.001
CAPS total score (mean±SD)	57.7±23.9	14.8±12.4	8.00	<0.001

CV+PTSD = combat veteran with PTSD, CV-PTSD = combat veteran without PTSD

CAPS = Clinician Administered PTSD Scale (Blake et al., 1995)

HDRS = 24-item Hamilton Depression Rating Scale (Hamilton, 1960)

[#] = University of Pennsylvania Smell Threshold Test (Doty, 2009)~ = Reduced detection compared to published norms (*M*=-6.17, *SD*=±1.4, *ps*<.001; Doty, 2009)

TST = Time since combat-related index trauma

^{*} = Combat Exposure Scale (Keane et al., 1989)[§] = Associated "burning" odor(s) with combat experiences

Table 3.

Group means and standard deviations for odor-elicited ratings and physiological responses

	<u>CV+PTSD</u>	<u>CV-PTSD</u>	<u>Group Effect</u>
<i>Intensity</i>			
PG	7.3 (21.2)	3.7 (6.5)	F(1,45) = 0.67, ns
LAV	50.2 (30.8)	50.4 (25.9)	F(1,45) = 0.00, ns
SMK	71.7 (26.3)	43.9 (27.7)	F(1,45) = 12.42, p<.01
BR	71.8 (20.7)	54.0 (25.3)	F(1,45) = 6.85, p<.05
<i>Negative Valence</i>			
PG	3.4 (10.4)	3.0 (11.2)	F(1,45) = 0.01, ns
LAV	1.7 (3.3)	0.7 (1.9)	F(1,45) = 1.86, ns
SMK	57.3 (36.8)	33.4 (25.7)	F(1,45) = 6.80, p<.05
BR	37.6 (28.3)	18.6 (19.6)	F(1,45) = 7.29, p=.01
<i>PTSD Symptoms</i>			
PG	17.0 (27.7)	10.1 (17.4)	F(1,45) = 1.08, ns
LAV	19.9 (29.9)	4.0 (12.3)	F(1,45) = 5.88, p<.05
SMK	41.3 (37.6)	19.8 (27.0)	F(1,45) = 5.15, p<.05
BR	49.1 (44.5)	14.3 (24.5)	F(1,45) = 11.36, p<.01
<i>in HR (BPM)</i>			
PG	4.4 (6.5)	5.2 (6.2)	F(1,45) = 0.18, ns
LAV	4.1 (5.2)	7.4 (6.2)	F(1,45) = 3.87, p<.1
SMK	5.1 (6.9)	7.9 (7.2)	F(1,45) = 1.79, ns
BR	2.2 (8.8)	8.6 (7.8)	F(1,45) = 6.92, p<.05
<i>in SCL (μS)</i>			
PG	0.17 (0.22)	0.31 (0.27)	F(1,45) = 3.92, p<.1
LAV	0.30 (0.34)	0.26 (0.30)	F(1,45) = 0.08, ns
SMK	0.29 (0.37)	0.33 (0.28)	F(1,45) = 0.22, ns
BR	0.32 (0.39)	0.40 (0.38)	F(1,44) = 0.52, ns

CV+PTSD = combat veteran with PTSD, CV-PTSD = combat veteran without PTSD

PG = odorless propylene glycol, LAV = lavender, SMK = cigarette smoke, BR = burning rubber

= baseline-corrected change

Heart Rate (HR) in beats per minute (BPM)

Skin Conductance Level (SCL) in microSiemens (μS)

ns = nonsignificant at p>.1

Table 4.
Pearson correlations between BR odor-elicited changes in HR and SCL, and clinical and odor variables.

Variables	Combat veterans with PTSD (CV+PTSD; n=22)									Combat veterans without PTSD (CV-PTSD; n=25)								
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
(1) BR odor-elicited HR	1									1								
(2) BR odor-elicited SCL	0.03	1								0.39 [^]	1							
(3) CAPS total score	0.05	0.15	1							0.22	0.14	1						
(4) HDRS score	0.15	0.16	0.71 ^{**}	1						-0.03	0.12	0.57 ^{**}	1					
(5) Time since index combat trauma	-0.58 ^{**}	-0.45 [*]	-0.30	-0.11	1					-0.05	-0.15	0.03	0.22	1				
(6) Odor function (detection) [#]	-0.56 ^{**}	-0.12	-0.10	-0.31	0.39 [^]	1				-0.45 [*]	-0.29	-0.18	0.04	0.08	1			
(7) BR odor (intensity)	-0.04	-0.14	-0.33	-0.38 [^]	0.07	0.21	1			0.07	0.12	0.04	-0.02	-0.40 [*]	-0.10	1		
(8) BR odor (negative valence)	0.11	0.03	-0.20	-0.25	-0.18	-0.17	0.57 ^{**}	1		0.21	0.26	-0.07	-0.16	0.03	-0.43 [*]	0.20	1	
(9) BR odor-elicited PTSD	-0.41 [^]	-0.17	0.01	0.08	0.43 [*]	0.19	0.14	0.36	1	0.46 [*]	0.40 [*]	0.35 [^]	0.16	0.08	-0.57 ^{**}	0.16	0.37 [^]	1

BR = burning rubber; HR = heart rate; SCL = skin conductance level

CAPS = Clinician Administered PTSD Scale; HDRS = 24-item Hamilton Depression Rating Scale

[#] higher score = reduced detection/sensitivity

^{*} = Pearson correlation significant at p<.05 (2-tailed);

^{**} = Pearson correlation significant at p<.01 (2-tailed)

[^] = Pearson correlation trend at p<.1 (2-tailed)