Neurophysiological Response to Olfactory Stimuli in Combat Veterans With Posttraumatic Stress Disorder

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Abstract: There is a need for a better understanding of underlying pathology in posttraumatic stress disorder (PTSD) to develop more effective treatments. The late positive potential (LPP) amplitude from electroencephalogram has been used to assess individual differences in emotional reactivity. There is evidence that olfaction is particularly important in emotional processing in PTSD. The current study examined LPP amplitudes in response to olfactory stimuli in 24 combat veterans with PTSD and 24 nonmilitary/non-PTSD controls. An olfactometer delivered three negatively valenced odorants, with 12 trials of each delivered in a random order. The groups did not differ in LPP amplitude across odorants. However, within the PTSD group, higher Clinician-Administered PTSD Scale scores related to an increased LPP amplitude after diesel fuel and rotten egg, but not n_butanol, odorants. Results provide specific targets and theory for further research into clinical applications such as selection of idiographic odorants for use in virtual-reality exposure therapy.

Key Words: PTSD, late positive potential, olfaction, EEG, emotional reactivity

(*J Nerv Ment Dis* 2018;206: 423–428)

Posttraumatic stress disorder (PTSD) is a syndrome that occurs in a subset of individuals exposed to a traumatic event, and includes symptoms of re-experiencing, avoidance, alterations in cognition and mood, and hyperarousal that persist for at least 1 month (American Psychiatric Association, 2013). Research has shown that approximately 8% to 18.5% of veterans returning from the wars of Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn (OIF/OEF/OND) have been diagnosed with PTSD (Richardson et al., 2010; Smith et al., 2008). The most effective treatments for PTSD are the psychotherapy approaches of cognitive processing therapy and prolonged exposure; however, approximately 33% to 50% of military veterans do not achieve clinically meaningful symptom improvement after these treatments (Steenkamp et al., 2015). Therefore, there is an acute need for a better understanding of underlying pathology to the direct development of more effective treatments.

One underlying factor in PTSD, emotional dysregulation, has recently been highlighted as a promising target for treatment intervention (Cloitre et al., 2016; Dvir et al., 2014; Sheynin and Liberzon, 2017). The late positive potential (LPP) amplitude from electroencephalogram (EEG) has been used to assess individual differences in emotion response. The LPP is a slow positive voltage potential that emerges around 350 milliseconds after stimulus onset, is maximal over parietal and central electrodes, and can continue for the duration of the stimulus and beyond (Hajcak et al., 2010). It is larger for emotional than neutral stimuli and is thought to represent the degree of sustained motivated attention (Hilgard et al., 2014; Schupp et al., 2000).

Two laboratories examined the LPP amplitude after negatively valenced pictures in combat veterans with PTSD and found no difference when compared with control groups during baseline conditions (Fitzgerald et al., 2016; Woodward et al., 2015). Another study that examined only a combat-related PTSD group found that the veterans with more severe PTSD symptoms showed a smaller LPP amplitude to angry faces, but no symptom to LPP relationship was found for happy or fearful faces (DiGangi et al., 2017). A second study reported a similar finding at a group level, as a group of combat veterans with PTSD showed a smaller LPP amplitude to angry, but not fearful, faces, as compared with veterans without PTSD (MacNamara et al., 2013). A prospective study found that a larger LPP amplitude to unpleasant pictures predicted more externalizing symptoms after exposure to a hurricane (Kujawa et al., 2016). Finally, nonpsychiatric participants scoring higher on a self-report scale of posttraumatic stress symptoms showed a larger LPP amplitude to negatively valenced pictures (Lobo et al., 2014).

A recent review provides converging evidence that olfaction plays a key role in emotional processing and memory in PTSD (Daniels and Vermetten, 2016), likely through aversive conditioning from odors associated with the trauma (Li, 2014). However, relatively little research has been done using olfactory stimuli in PTSD as compared with other sensory modalities (Daniels and Vermetten, 2016). Most of the existing literature on LPP, in both nonpsychiatric and psychiatric samples, have used visual stimuli, and, to the authors' knowledge, none have examined the LPP in direct response to olfaction. However, in nonpsychiatric adults, stress-related odors can enhance LPP amplitude after simultaneous presentation of negative visual stimuli (Kastner et al., 2016; Rubin et al., 2012).

The current study examined whether LPP amplitude after negatively valenced odorants in combat veterans with PTSD is larger than in a nonmilitary/non-PTSD control group. There does not seem to be existing literature to directly inform hypotheses. Although two studies that examined PTSD and control samples at a group level found no difference in LPP amplitude after emotional pictures were shown (Fitzgerald et al., 2016; Woodward et al., 2015) and two reported a smaller LPP amplitude to pictures of angry faces in particular (DiGangi et al., 2017; MacNamara et al., 2013), these studies did not assess olfactory stimuli. Therefore, our hypothesis was that, given the importance of olfaction in PTSD (Daniels and Vermetten, 2016), the PTSD group would show an increased LPP amplitude in response to a trauma-related scent, as compared with a control group. Given the existing but conflicting findings regarding relationships between symptom severity and LPP amplitude (DiGangi et al., 2017; Kujawa et al., 2016; Lobo et al., 2014), we included exploratory analyses of these relationships.

METHODS

Participants

We recruited military veterans from the OIF/OEF/OND wars through advertisements and clinician referrals. Veteran participation

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This study was supported by the US Army Medical Research & Materiel Command-Military Operational Medicine Research Program (USAMRMC-MOMRP; contract W81XWH-11-2-0038) to Drs Bedwell, Beidel (PI), Bohil, and Neider. The study had both MRCM HRPO and local IRB approval and does not necessarily reflect the policy/position of the government. The funding source had no involvement with the design, collection, analysis or interpretation of the data, or the writing of the report or the decision to submit the article for publication.

ISSN: 0022-3018/18/20606–0423

DOI: 10.1097/NMD.0000000000000818

TABLE 1. Demographic and Clinical Characteristics

Group	*N*	Age	% Non-Hispanic Caucasian	UPSIT Total Score	CAPS Total Score
Controls	24	26.92 (9.32); range = 18–57	75%	34.83 (2.71)	NA
PTSD	24	36.83 (8.26); range = 26–57	67%	35.38 (2.53)	97.79 (14.43); range = 65–127

Note: All participants in the study were male. Continuous data are presented as mean (SD).
NA indicates not applicable.

was contingent on entering a 3-week exposure-based treatment for combat-related PTSD. The clinical intervention and outcome data are reported elsewhere (Beidel et al., 2017b), as the present study focuses on the baseline LPP amplitude relationships before treatment. We also recruited a nonmilitary/non-PTSD control group. For the veteran group, inclusion criteria included being a male older than 17 years with a primary diagnosis of combat-related PTSD for at least 6 months. Exclusionary disorders included current substance use disorders, antisocial personality disorder, and psychotic disorders. Inclusion criteria for the control group included being a male older than 17 years, and exclusionary diagnoses included PTSD along with the same diagnoses listed for the veteran group. In both groups, exclusionary criteria also included a score of less than 30 on the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984).

We excluded veteran participants because of a low UPSIT score ($n = 2$), not having primary combat-related PTSD ($n = 5$), missing excessive behavioral ratings ($n = 1$), and problems with EEG ($n = 9$)—resulting in 24 veteran participants for analyses. We excluded control group participants because of exclusionary diagnosis ($n = 1$), low UPSIT score ($n = 1$), and excessive artifact in EEG ($n = 7$)—resulting in 24 control participants for analyses. Participants received monetary compensation for participation in the study. See Table 1 for the characteristics of the samples.

Procedures

The Clinician-Administered PTSD Scale (CAPS; Weathers et al., 2001) was used to determine the presence and severity of PTSD. The CAPS is a semistructured interview that produces a dimensional total score. The Structured Clinical Interview for *DSM-IV,* Clinician Version (First et al., 1997b) and Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders, Self-Report (First et al., 1997a) assessed other *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*) diagnoses in the veteran group. For the control participants, the MINI International Neuropsychiatric Interview (Sheehan et al., 1997) examined the presence of *DSM-IV* diagnoses. Final diagnoses were determined by two licensed psychologists with extensive experience in PTSD assessment.

An air compressor and Scentroid SC300 mobile olfactometer (IDES Canada, Inc) was used to present three liquid odorants chosen to represent neutral, negative, and trauma-related valences. For the trauma-related odor, we selected a standardized trauma cue of diesel fuel (0.75 mL, with dilution of 16) based on previous success in symptom provocation and positron emission tomography activation of the emotion circuit in combat veterans with PTSD (Vermetten et al., 2007). We chose a rotten egg odorant (1 μL, with dilution of 4) as the non–trauma-negative scent, as it is commonly used as a negatively valenced scent in other studies (Hummel et al., 2010; Schredl et al., 2009). Finally, we chose n_butanol (1 μL, with dilution of 12), which has a faint alcohol odor, to be a standard comparison odorant based on frequent use for determining olfactory thresholds (*e.g.*, Sniffin' Sticks; Kobal et al., 2000). We received liquid samples of these odorants from the manufacturers of the mobile olfactometer (IDES Canada, Inc). A smell port was placed 2 cm from the participant's nose using a flow rate of 8 L/min and was connected to the olfactometer with a 636-cm tube.

The three scents were presented in a random order with 12 trials of each scent. The paradigm consisted of 20 seconds of rest and delivery of fresh air, scent delivery for 7 seconds, 10 seconds of rest and delivery of fresh air, and a subjective rating prompt for 12 seconds. If a participant did not enter a rating in 12 seconds, the task continued. All participants were missing less than 10% of total response cues. Participants entered ratings using a mouse and computer monitor on hedonic tone (*i.e.*, valence; pleasantness versus unpleasantness) and intensity (weak versus strong). The ratings were similar to those used in German Standard VDI 3882 (Frechen, 2000). Valence ratings ranged from −4 ("offensive") to +4 (very pleasant); intensity ratings ranged from 0 ("not detectable") to 6 ("intolerable") (see Figure 1).

EEG was recorded using an EEGO Sports amplifier (ANT Neuro, Netherlands) and a customized NIRScap (Brain Vision LLC, Morrisville, NC), which included 29 recorded electrodes (Fp1, Fp2,

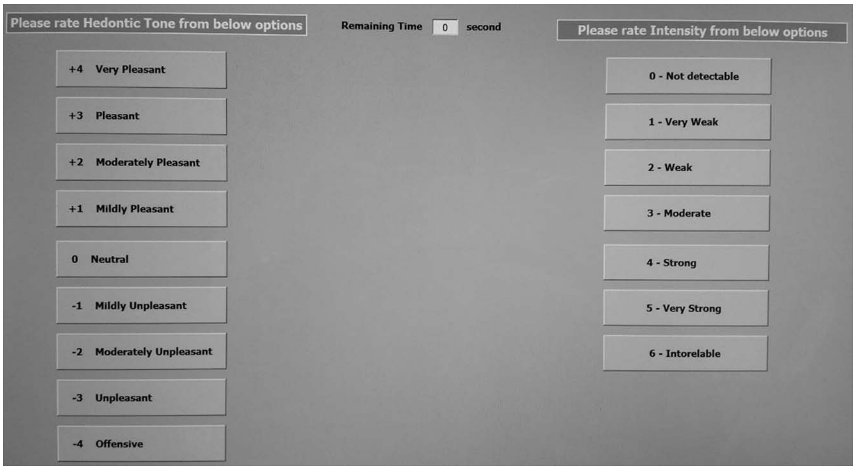

FIGURE 1. Depiction of the behavioral rating screen presented during the task.

F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, Pz, POz, Iz, FC1, FC2, CP1, CP2, FC5, FC6, CP5, and CP6). POz was used as the active reference during recording. The EEG was recorded at 500 Hz with no filters and processed using Brain Vision Analyzer 2.1.2 (Brain Products GmbH, Munich, Germany). Infinite impulse response filters were applied offline using a high-pass cutoff of 0.10 Hz (order 2 roll-off) and a low-pass filter of 30 Hz (order 2 roll-off). The data was segmented from −1000 to 2500 milliseconds relative to the onset of each scent. As ocular electrodes were not available, we used a linear derivation from electrodes FP1 and FP2 to correct the remaining scalp electrodes for blinks, using independent component analysis. We re-referenced the 29 remaining electrodes to their common average and POz was then included as an active electrode of interest. A baseline correction of −1000 to 0 milliseconds was applied, followed by artifact rejection for segments that exceeded ±120 μV. Average waveforms were created using the 12 possible segments for each of the scents.

Examination of voltage topography maps, created from the grand average across all participants and odorants, revealed a sustained positive deflection 400 milliseconds after release of the odorant that had a predominantly parieto-occipital distribution (see Figure 2). From this topography, we chose to create a linear derivation from electrodes POz, O1, O2, and Iz to use for measurement of LPP. Consistent with recommendations from others (Hajcak et al., 2010), we defined early and late windows of the LPP. Based on inspection of the grand average waveform from all scents and participants from our LPP electrode cluster (see Figure 3), we decided to start the early window at 500 milliseconds and extended it to 1500 milliseconds. We chose a late window of 1500 to 2500 milliseconds. We excluded electrodes from the linear derivation used to measure LPP if there was less than 10 remaining segments remaining for a given odor condition after artifact rejection, which is greater than the 8 minimal trials recommended for acceptable reliability in the averaged LPP waveform (Moran et al., 2013). We then excluded from data analysis participants analysis who had more than one of the four LPP electrodes removed from the linear derivation. We extracted the average voltage from each of the two time windows from the linear derivation of electrodes POz, O1, O2, and Iz for use in the statistical analyses.

Statistical Analyses

See Tables 2 and 3 for descriptive statistics for the behavioral ratings and LPP amplitudes by group. As there were several variables across both behavioral ratings and LPP amplitudes with kurtosis values greater than 2.5, along with a modest sample size, we chose to use nonparametric statistics across analyses. The control group was significantly younger than the veterans, $t(46) = 3.90$, $p < 0.001$; however, across all participants, age did not show a significant relationship with any behavioral rating or LPP amplitude (all $ps > 0.07$). The groups did

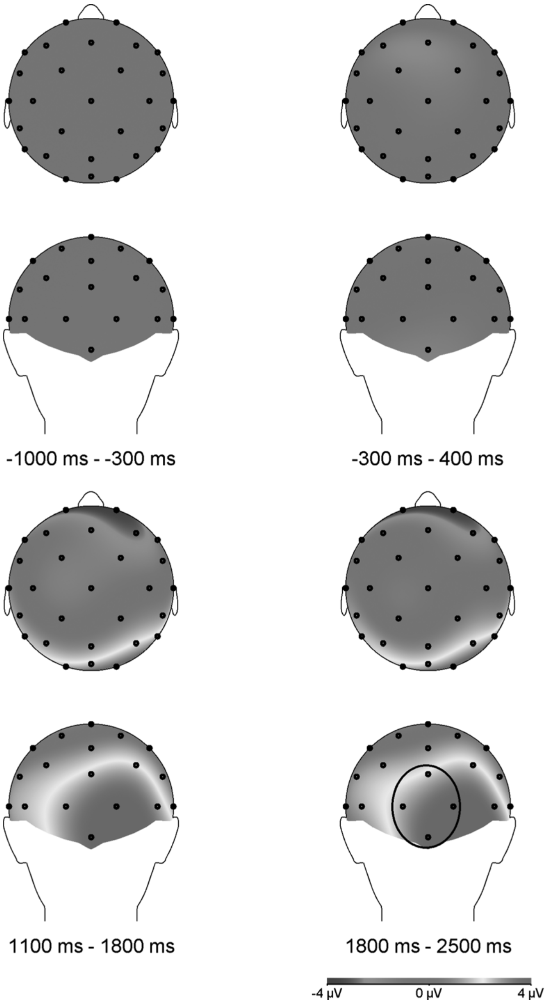

FIGURE 2. Voltage topography map across all odorants and participants. The black circle in the last image represents the four electrodes that were chosen to average for LPP measurement (POz, O1, O2, and Iz).

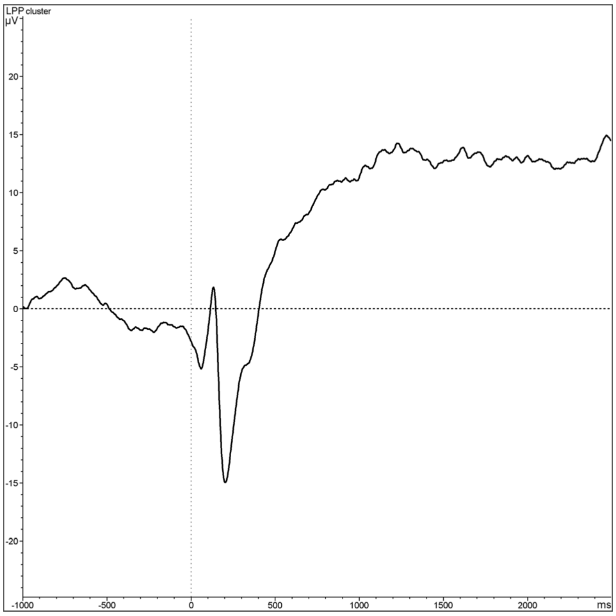

FIGURE 3. Grand average waveform for the LPP across all odorants and participants. Includes an additional 7 Hz low-pass filter.

not differ on UPSIT scores, years of education, or race/ethnicity categories (all ps > 0.09).

RESULTS

Mann-Whitney U tests were used to examine group differences for the behavioral ratings of each odorant. As shown in Table 2, compared with controls, the PTSD group reported an increased negative valence rating for the rotten egg odorant and a decreased intensity rating for the diesel fuel scent. A related-samples Friedman test across all participants revealed a significant main effect of odorant for valence ratings, $\chi^2(2, N = 48) = 16.80, p < 0.001$. Pairwise comparisons with Wilcoxon signed-ranked tests revealed that the rotten egg odorant was rated significantly less negative in valence than both n_butanol, $Z = 3.95$, $p < 0.001$, and diesel fuel, $Z = 2.93, p = 0.003$, which did not differ from each other, $Z = 0.74, p = 0.46$. A parallel analysis showed that intensity ratings also showed a significant main effect, $\chi^2(2, N = 48) = 32.18$, $p < 0.001$. The same pattern was found as with valence, as the intensity ratings for the rotten egg odorant were lower than both n_butanol, $Z = 4.69$, $p < 0.001$, and diesel fuel $Z = 4.57$, $p < 0.001$, which did not differ from each other, $Z = 0.06, p = 0.96$. One-sample t-tests across all participants revealed that all odorants were rated as negative in valence and detectable in intensity (all ps < 0.001).

Spearman correlations examined the relationship between the two behavioral ratings with the LPP amplitude from the two time windows within each odorant, across all participants. Only one of these correlations was statistically significant—a less negative/more positive valence rating for the rotten egg odorant related to a greater LPP amplitude during the early time window, $r_s(48) = 0.32, p = 0.03$ (all other ps > 0.07).

Mann-Whitney U tests examined group differences for the LPP amplitude of each odorant within each of the two LPP time windows. There were no statistically significant group differences for LPP amplitudes (all ps > 0.07; see Table 3 for descriptive statistics). Related-samples Friedman tests across all participants revealed that LPP amplitude did not differ by odorant for the early, $\chi^2(2, N = 48) = 4.29, p = 0.12$, or late, $\chi^2(2, N = 48) = 2.54, p = 0.28$, time windows.

Within the veterans group, Spearman correlations of the six behavioral ratings (three odorants by two rating types) and the CAPS total score revealed that a higher CAPS total score related to a higher intensity rating for the rotten egg odorant, $r_s(24) = 0.42, p = 0.04$ (all other ps > 0.05). Spearman correlations of the six LPP amplitudes (three odorants by two LPP time windows) and the CAPS total score revealed a positive relationship with the early LPP amplitude for diesel fuel, r_s $(24) = 0.43, p = 0.04$, and the late LPP amplitude for rotten egg, r_s $(24) = 0.41, p = 0.05$ (all other ps > 0.09). Thus, veterans with more severe PTSD symptoms showed a larger early LPP response to the diesel fuel odorant (see Figure 4) and a larger late LPP response to the rotten egg odorant.

DISCUSSION

Our first hypothesis was not supported, as there were no group-level differences in LPP amplitude to any odorant between veterans with PTSD and controls. However, our planned exploratory symptom-level analyses found that greater severity of PTSD symptoms in the veterans related to increased early window LPP amplitude to the diesel fuel odorant (see Figure 4) and increased late window LPP amplitude to the rotten egg odorant. It is interesting that the diesel fuel odorant showed this relationship, as this odorant was most likely to relate to the trauma. Although only a minority of our participants reported a diesel fuel scent as a direct feature of their trauma ($N = 8$; *e.g.*, vehicle explosion), the scent of diesel fuel has been reported as pervasive in deployment locations such as Iraq (Stuart et al., 2002) and was previously rated as more distressing by combat veteran samples with PTSD than by controls (Cortese et al., 2015; Vermetten et al., 2007). However, as a similar finding emerged with the rotten egg odorant, this suggests a more generalized hyperarousal to at least some negatively valenced odorants that are not related to a trauma.

TABLE 2. Descriptive Statistics for the Behavioral Ratings of the Odorants

	Valence Rating			Intensity Rating		
Group	**n_butanol**	**Rotten Egg**	**Diesel Fuel**	**n_butanol**	**Rotten Egg**	**Diesel Fuel**
Controls	−1.11 (0.82)	−0.47 (0.76)**	−0.94 (1.08)	3.11 (0.81)	2.44 (0.74)	3.25 (0.88)
PTSD	−1.30 (1.33)	−1.09 (0.91)	−1.38 (0.94)	3.02 (0.92)	2.54 (1.03)	2.87 (1.08)*
All participants	−1.20 (1.10)	−0.78 (0.89)[a]	−1.16 (1.03)	3.06 (0.86)	2.49 (0.89)[a]	3.06 (0.99)

Note: Data are presented as mean (SD). Valance ratings ranged from −4 ("offensive") to +4 (very pleasant). Intensity ratings ranged from 0 ("not detectable") to 6 ("intolerable").

*$p < 0.05$, between groups; based on Mann-Whitney U tests.

** $p < 0.01$ between groups; based on Mann-Whitney U tests.

[a] Rated significantly less negative in valence and less intense than other two odorants (all ps < 0.01), which did not differ from each other; based on Wilcoxon signed-ranked tests.

TABLE 3. Descriptive Statistics for the LPP Mean Amplitudes (μV) Elicited From the Odorants

	Controls	PTSD	All Participants
Early LPP window (500–1500 ms)			
n_butanol	7.57 (13.97)	11.53 (26.22)	9.55 (20.88)
Rotten egg	12.94 (16.53)	11.79 (18.08)	12.37 (17.15)
Diesel fuel	11.19 (12.81)	11.10 (20.41)	11.14 (16.86)
Late LPP window (1500–2500 ms)			
n_butanol	11.13 (22.50)	13.94 (25.22)	12.54 (23.69)
Rotten egg	18.00 (18.89)	9.37 (21.02)	13.69 (20.24)
Diesel fuel	12.37 (14.00)	6.41 (28.17)	9.39 (22.21)

Note: Mean amplitude represents the average amplitude in μV within the stated time window. There were no statistically significant group differences for LPP amplitude by odorant within either LPP window based on Mann-Whitney *U* tests. Across the entire sample, there were no statistically significant differences for LPP amplitude across odorants within either time window based on related-samples Friedman tests.

The PTSD group also rated the rotten egg odorant as more negative in valence than controls did and increased PTSD symptom severity related to an increased intensity rating of that odorant. In contrast, the PTSD group rated the diesel fuel odorant as less, rather than more, intense than controls, and behavioral ratings of diesel fuel did not relate to symptom severity. Thus, although the behavioral ratings were generally consistent with LPP findings for the rotten egg odorant, there was discrepancy between these subjective and objective measures for diesel fuel. It is possible that in participants with more severe PTSD, the hyperarousal reaction to the diesel fuel odorant (as indexed by the LPP) may have occurred on a relatively more subconscious level compared with the rotten egg odorant. Further research can explore this possibility with a wider range of odorants that vary in specificity to the participant's idiographic trauma cues.

Our lack of a group-level difference in LPP amplitude is consistent with two previous studies that reported no difference in LPP response to visual stimuli between PTSD and control groups (Fitzgerald et al., 2016; Woodward et al., 2015). However, we expected that our novel use of olfactory stimuli would be more sensitive to group-level differences than visual stimuli used in previous studies. A previous study found that veterans with PTSD showed a reduced LPP amplitude to angry, but not fearful, faces compared with veterans without PTSD (MacNamara et al., 2013). However, a reduction in LPP amplitude may be specific to threat reactivity (*e.g.*, viewing faces depicting anger), particularly as a similar finding, specific to angry faces, was found at the PTSD symptom level by another laboratory (DiGangi et al., 2017). Another explanation for the null findings at the group level of analysis in the present study and others is the lack of idiographic trauma cues, individualized for each participant. Although it does not appear that research has examined whether generalized or idiographic trauma cues show more robust effects with LPP to emotional stimuli, a meta-analysis suggested that idiographic cues relate to a broader range of psychophysiological correlates in PTSD samples (Pole, 2007). As odors are beginning to be integrated into virtual reality exposure therapy for PTSD (Beidel et al., 2017a; Daniels and Vermetten, 2016), a baseline assessment of LPP amplitude response to a variety of odorants related to the reported trauma may be helpful in selecting one or more ideal odorants for use in the exposure therapy.

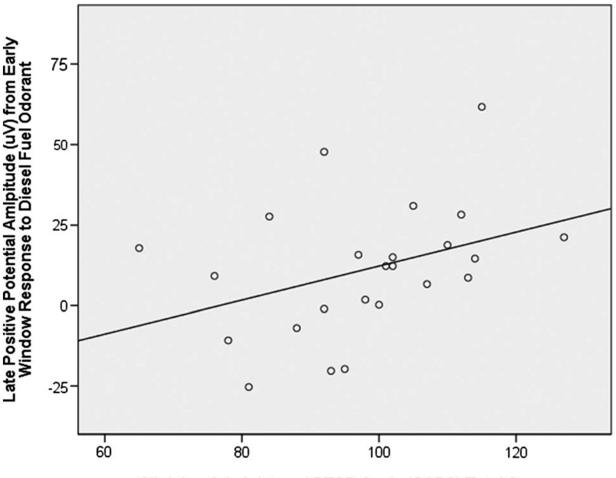

FIGURE 4. Scatterplot depicting the relationship of the LPP amplitude (during early window) to the diesel fuel odorant and severity of symptoms in the PTSD group. $r_s(24) = 0.43$, $p = 0.04$.

Although the present study is novel in that it seems to be the first to examine the LPP using olfactory stimuli in a PTSD sample, it also has limitations. The sample size was modest, only men were included, and there was no positively valenced comparison odorant. Although we were hoping that the standard reference odorant of n_butanol would be relatively neutral in valence, it was rated as equally negative in valence as the diesel fuel odorant. This may be a result of olfaction being inherently affective in perception as compared to other senses (Khan et al., 2007), making it difficult, if not impossible, to identify a globally "neutral" scent. In addition, our findings involving symptom severity are exploratory, given the relative paucity of related previous research to inform a hypothesis. However, results provide specific targets and theory for further research in this area.

CONCLUSIONS

There were no group-level differences between combat veterans with PTSD and nonmilitary/non-PTSD controls on LPP amplitude response across three negatively valenced odorants. However, within the PTSD group, participants with more severe clinician-rated symptoms showed a greater LPP amplitude in response to two of the three odorants—diesel fuel and rotten egg. Subjective ratings of the odorants generally corresponded with LPP amplitude relationships with PTSD for the rotten egg, but not the diesel fuel, odorant.

DISCLOSURE

The authors declare no conflict of interest.

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