Behavioural Brain Research 396 (2021) 112914

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Neurophysiological responses to safety signals and the role of cardiac vagal control

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ARTICLE INFO

Keywords:
Safety
Signals
Startle
Event-related potentials
Vagal control
PTSD

ABSTRACT

Background: Deficits in safety signal learning are well-established in fear-related disorders (e.g., PTSD, phobias). The current study used a fear conditioning paradigm to test associations among eye blink startle and event-related brain potential (ERP) latency measures of safety signal learning, as well as the role of cardiac vagal control (a measure of top-down inhibition necessary for safety learning).

Methods: Participants were 49 trauma-exposed women ages 17 to 28 years. Eyeblink startle response and ERP amplitudes/latencies were derived for conditioned stimuli associated (CS+) and not associated (CS-) with an aversive unconditioned stimulus. ERPs included the P100 and late positive potential (LPP), which index early visual processing and sustained emotional encoding, respectively. Cardiac vagal control was assessed with resting heart rate variability (HRV).

Results: P100 and LPP latencies for the CS- (safety signal stimulus) were significantly negatively associated with startle to the CS-, but not the CS + . LPP CS- latencies were significantly negatively associated with PTSD Intrusion scores, and this relationship was moderated by vagal control, such that the effect was only present among those with low HRV.

Conclusions: ERP-based markers of safety signal learning were associated with startle response to the CS- (but not CS+) and PTSD symptoms, indicating that these markers may have relevance for fear-related disorders. Cardiac vagal control indexed by HRV is a moderating factor in these associations and may be relevant to safety signal learning.

1. Introduction

One of the most enduring characteristics of fear-related disorders is a decreased ability to inhibit fear in safe situations. Sometimes referred to as safety signal learning, this process involves top-down inhibition of sympathetic arousal when confronted with non-threatening stimuli. Among individuals exposed to trauma, an example of safety signal learning is the inhibition of fear when confronted with an individual who looks familiar to a prior assailant (i.e., there may be some initial arousal but this quickly subsides when the individual realizes they are not in danger). In contrast, an individual with posttraumatic stress disorder (PTSD) may not be able to inhibit their fear response and may experience prolonged arousal and fear despite the lack of threat. Similarly, individuals with panic disorder experience deficits in their ability to inhibit fear of non-dangerous physical sensations and interoceptive cues (e.g., increased heartbeat during exercise) and those with phobic disorders experience deficits in fear inhibition for a range of non-dangerous objects or situations (e.g., heights, insects, blood). Research in these populations has demonstrated that poor safety signal learning is a specific phenotype of fear-related disorders that differentiates them from healthy populations (e.g., [1,2–4]).

Safety signal learning can be modeled with fear conditioning paradigms, such that one conditioned stimulus (CS; e.g., colored shape) is paired with an aversive unconditioned stimulus (US; e.g., shock, air

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https://doi.org/10.1016/j.bbr.2020.112914
Received 22 May 2020; Received in revised form 3 September 2020; Accepted 10 September 2020
Available online 22 September 2020

blast) while another CS is never paired. In this paradigm, the paired stimulus is referred to as the CS + and represents threat, while the unpaired stimulus is the CS- and represents the absence of threat (i.e., safety). Startle response to the CS + and CS- may be indexed by electromyography of the eye blink or by skin conductance level. Among individuals with posttraumatic stress disorder (PTSD) and panic disorder, startle responses to the CS- are elevated compared to controls, suggesting that these individuals exhibit deficits in safety signal learning [2,3,5]. Whereas the startle response is one of the primary assessment methods in fear conditioning paradigms, neurophysiological indices of fear and safety learning may also be used, with the advantage of providing a means to probe underlying brain mechanisms with time resolution that is in the milliseconds range.

Prior electrophysiology research in fear conditioning has focused on event-related potentials (ERPs) such as the P100, the P300, and the late positive potential (LPP). The P100 ERP has been implicated in early visual processing and its amplitudes tend to be higher for fearful stimuli (e.g., threatening faces) compared to neutral or positive stimuli [6,48], suggesting that increased visual system activity is associated with increased salience of visual cues. The P300 and LPP are later ERP components reflecting more sustained emotional encoding of stimuli and generally appear greater for emotionally salient information across a variety of samples [7–11,42]. They are also heightened in response to aversive, unpleasant, and threatening stimuli compared to neutral and safe stimuli among healthy samples [12–15] and those with PTSD [16]. Our group recently investigated the LPP with trauma-exposed undergraduates using a fear conditioning paradigm and found that LPP amplitudes were significantly greater in response to a CS + compared to a CS- [17].

Fewer studies have tested ERP latencies in fear-based disorders and findings have been mixed. Given that ERP latencies are extremely sensitive indicators of reaction time to emotional stimuli (in the millisecond range), they are important complementary indicators to ERP amplitudes. Specifically, latencies provide data regarding the speed of information processing, while amplitudes provide data regarding the emotional salience of the data processed. Individuals with PTSD demonstrate deficits in cognitive domains such as information processing (particularly related to safety; see [18] for a review); it is therefore important to better characterize this aspect of safety signal learning in trauma-exposed populations. Among individuals with panic disorder, P100 and P300 latencies appear to be shorter compared to controls across several stimulus types [19–21]. In PTSD, one study found that individuals with PTSD exhibited longer P300 latencies for happy faces compared to trauma-exposed controls [22], and another found that combat Veterans with PTSD exhibited longer P300 latencies for target images (animals) compared to healthy controls [23]. This may suggest that PTSD is associated with slower emotional processing of non-threatening stimuli; however, no prior study has tested ERP latencies for safety signals in the context of fear or aversive conditioning, which has relevance for fear-based disorders such as PTSD. Specifically, safety signal learning is one of the primary components in cognitive-behavioral treatments for PTSD, such as exposure therapy. ERP latencies for safety signals may therefore serve as indicators of which individuals will respond better to such treatments (e.g., those who respond to safety more rapidly) or as indicators of treatment response overall.

A natural extension from neurophysiological indices of inhibition or safety signal learning is cardiac vagal control because it indexes the influence of the vagus nerve (the 10th cranial nerve) on the heart's sinoatrial node. Thus, measures of vagal control, such as heart rate variability (HRV), represent top-down inhibition of sympathetic arousal controlled by the parasympathetic nervous system. HRV refers to the variability in timing between heart beats and greater variability is often associated with emotion regulation and general psychological health [24]. Among individuals with fear- and anxiety-based disorders, HRV tends to be lower at baseline [25–29] and in response to challenge [30–33], reflecting poor inhibition. Few studies have examined HRV simultaneously with startle during fear conditioning, but generally HRV appears to confer lower startle responses among healthy and undergraduate samples [34,54], as well as individuals with panic disorder [35]. One study specifically tested fear inhibition using startle and found that individuals with higher HRV exhibited better fear inhibition compared to those with lower HRV [36]. To our knowledge, no prior studies have tested HRV-related differences in neurophysiological indices of fear inhibition/safety signal learning. Given that HRV is a measure of cortical regulation of peripheral physiology and that individuals with PTSD exhibit deficits across these domains, it is critical to study the influence of HRV on neurophysiological indices. Further, the aforementioned studies suggest that HRV may influence startle responses to conditioning and thus should be considered when using these paradigms. As mentioned above, ERP latencies to safety signals could be useful indicators of treatment response; the influence of HRV on such measures is therefore important to capture as it may moderate ERP responses.

The current study used eyeblink startle and ERPs to probe safety signal learning and the role of HRV in a trauma-exposed sample. Since our prior work focused on P100 and LPP amplitudes and given the limited studies testing latency effects, the current study evaluated P100 and LPP latencies among the same sample [17]. Given that longer ERP latencies for neutral stimuli have been observed in PTSD samples, we hypothesized that 1) longer P100 and LPP latencies for a safety signal (CS-) would be significantly associated with increased eye blink startle response to the CS-; 2) longer P100 and LPP latencies for a CS- would be significantly associated with increased PTSD symptoms; and 3) HRV would moderate these associations, such that individuals with lower HRV (a risk factor for psychopathology) would demonstrate stronger associations between P100/LPP latencies and a) startle to the CS-, as well as b) PTSD symptoms.

2. Methods

2.1. Participants and Procedure

The sample included 49 trauma-exposed undergraduate females who were recruited from a Midwestern university ($M_{age} = 20.21$, $SD = 2.71$). In terms of race, 57.1% identified as White ($n = 28$), 26.5% identified as Black or African American ($n = 13$), 8.2% identified as Asian ($n = 4$), and 4.1% identified as Other ($n = 2$); two participants chose not to respond. Most participants identified as non-Latino/Hispanic (89.8%).

Potential participants were invited via email to participate as part of their psychology courses; interested students were then contacted and scheduled. Following informed consent procedures, participants completed self-report measures and then underwent a fear conditioning paradigm with concurrent electroencephalogram (EEG) recording. Participants received course credit for their participation, and procedures were approved by the university's Institutional Review Board.

2.2. Measures

2.2.1. Traumatic Life Events Questionnaire

The Traumatic Life Events Questionnaire (TLEQ; [47]) is a brief measure of trauma exposure. Respondents indicate the frequency of experiencing 22 potentially traumatic events (e.g., physical abuse, sexual assault, natural disaster).

2.2.2. PTSD Checklist – 5

The PTSD Checklist – 5 (PCL-5; [55]) is a 20-item self-report measure of PTSD symptoms that corresponds to the four DSM-5 symptom clusters. These clusters include: Intrusions (Criterion B; 5 items), Avoidance (Criterion C; 2 items), Negative Alterations in Cognition and Mood (Criterion D; 7 items), and Alterations in Arousal and Reactivity (Criterion E; 6 items). Items are rated on a 5-point Likert-type scale from

0 (*not at all*) to 4 (*extremely*), with higher scores indicating worse PTSD symptoms. Cronbach's alphas in the current sample were .81 (Intrusion), .86 (Avoidance), .90 (Negative Alterations in Cognition and Mood), and .89 (Alterations in Arousal and Reactivity).

2.3. Fear Conditioning Paradigm

The fear conditioning paradigm used was a fear-potentiated startle (FPS) paradigm, which has previously been validated [2,44,50]. In the FPS paradigm, an aversive unconditioned stimulus (US; 140 psi airblast to the larynx) was repeatedly paired with a conditioned stimulus (CS+; a blue square presented on computer screen), while a different shape (a purple triangle) was never paired with the aversive stimulus (CS-). The paradigm included a 108-dB startle probe that elicited the eyeblink acoustic startle response. The startle probe was presented during CS + and CS- trials, and on its own (noise alone [NA] trials) to assess individual baseline startle response. The startle probe was presented 6 seconds after initiation of the CS and was followed by the US 0.5 seconds later. The acquisition phase of the paradigm consisted of one habituation block in which no airblasts were delivered, followed by three conditioning blocks with four trials of each type in each block (i.e., 12 CS + trials, 12 CS- trials, 12 NA trials). The extinction phase occurred 10 min after acquisition and consisted of four blocks with four trials of each type, and the airblast was no longer paired with the CS + . The inter-trial interval was between 9 and 22 seconds. EEG data were continuously recorded during the FPS session (see below).

2.4. Physiological Data Acquisition and Processing

Biopac MP150 for Windows (Biopac Systems, Inc.) was used to collect physiological data at a sampling rate of 1 kHz, amplified and digitized using the Biopac system. Eyeblink signals (electromyogram; EMG) were amplified by a gain of 1000. Screening of eyeblinks involved visually inspecting EMG data for double blinks and other artifacts. When necessary, segments of EMG data without an identifiable eyeblink were deleted. No participants had fewer than 75% usable EMG segments and therefore all participants were included in EMG analyses. Startle magnitude values were obtained for each stimulus (e.g., amplitude of eyeblinks in response to each CS) using MindWare software. FPS was calculated using a difference score ([startle magnitude in the presence of a CS in each conditioning block] – [startle magnitude to startle probe alone]); [49]. Specifically, two FPS variables were calculated: FPS to the CS + during late acquisition (average of blocks 2 and 3) and FPS to the CS- during late acquisition (average of blocks 2 and 3).

HRV was also processed using MindWare software, which identifies electrocardiogram (ECG) recorded R-waves and R-R intervals (i.e., the time period between heart beats), and detects artefacts, which were manually inspected and corrected. HRV was derived by spectral analysis of one-minute epochs with a Hamming windowing function and log transformed. Settings for the high frequency band were based on standard recommendations for HRV data (0.12–0.40 Hz; Task Force, 1996). HRV values were averaged from the habituation/baseline phase prior to startle probes and fear conditioning.

2.5. EEG Data Acquisition and Processing

EEG data were continuously recorded during the FPS session from 9 International 10–20 system sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with a tin-electrode cap (Electro-Cap International Inc., Eaton, OH). We excluded Pz from analyses due to an equipment failure at the Pz site. Electrode impedances were kept below 5 kΩ. Horizontal and vertical eye movements were recorded using electrooculogram (EOG) with electrodes placed at the outer canthi and lower orbital ridges. Each EEG and EOG channel was amplified by separate EEG100C and EOG100C modules (Biopac MP100C system, Biopac Systems, Goleta, CA) with an analog bandpass filter from 0.1 to 35 Hz. EEG and EOG data were sampled at 1 kHz (1,000 samples/sec) and a 60 Hz notch filter was applied. EEG and EOG data were gathered using AcqKnowledge 3.8.1 for the Biopac MP100C system.

EEG data were processed with BrainVision Analyzer 2.04 software (Brain Products, Germany) and referenced to the average reference, with offline filters (0.1-30 Hz) applied. Independent component analysis (ICA) was used to identify and remove eye movement and eyeblink artifacts. The following criteria were used for the ICA: whole data, classic PCA sphering, infomax ICA, energy ordering, and 512 convergence steps. For each trial, EEG data were segmented 200 ms before and 1,200 ms after stimulus onset. Consistent with prior research [42], a semi-automated procedure to reject intervals for individual channels used the following criteria: (a) a voltage step > 50 μV between sample rates, (b) a voltage difference > 300 μV within a trial, and (c) a maximum voltage difference of < 0.50 μV within a 100 ms interval. In addition to these semi-automated procedures, all trials were visually inspected for manual artifact identification and removal. Three participants were removed from analyses due to poor EEG data quality. P100 and LPP latencies for the CS + and CS- were determined by selecting the time (ms) at which each ERP reached its peak during the given timeframe at Cz (i.e., 75-125 ms poststimulus for the P100, 600-1200 ms poststimulus for the LPP).

3. Results

Descriptive statistics and bivariate correlations among all study variables are summarized in Table 1. As described in our prior work [17], P100 and LPP latencies for the CS + and CS- did not differ significantly (see Fig. 1 for CS + and CS- waveforms). Contrary to our expectations, startle response to the CS- was significantly *negatively* associated with CS- latencies for both the P100 (r = -.417, p = .004; Fig. 2, top panel) and the LPP (r = -.316, p = .033; Fig. 2, bottom panel), suggesting that longer visual processing and emotional encoding conferred *better* safety signal learning (i.e., decreased CS- startle). Similarly, LPP latencies for the CS- were significantly *negatively* associated with scores on the Intrusions (r = -.303, p = .036; Fig. 3, top panel) and Negative Alterations in Cognition and Mood (r = -.304, p = .036; Fig. 3, bottom panel) symptom clusters. Neither P100 nor LPP latencies for the CS + were associated with startle to the CS+/CS- or with PTSD symptom clusters.

In order to test moderation by HRV, we conducted hierarchical linear regressions only for variables that were significantly related at the bivariate level. Variables used to create interaction terms were mean-centered and then multiplied by one another. In the first regression model, P100 latency to the CS- was significantly associated with CS- startle (β = -.43, p = .004), but baseline HRV (β = .07, p = .598) and the P100 latency x HRV interaction (β = -.14, p = .320) were not. In the second model, LPP latency to the CS- was significantly associated with CS- startle (β = -.33, p = .031), but baseline HRV (β = .10, p = .517) and the LPP latency x HRV interaction (β = -.08, p = .588) were not. For PTSD symptoms, Negative Alterations in Cognition and Mood were not significantly predicted by LPP latency (β = -.26, p = .074), HRV (β = .09, p = .552), or their interaction (β = .24, p = .104). Symptoms on the Intrusions cluster were significantly associated with LPP latency to the CS- (β = -.29, p = .041) and the LPP latency x HRV interaction (β = .29, p = .043; Table 2). To clarify the interaction effect, simple slopes analyses were conducted at high and low HRV levels (calculated by subtracting and adding one standard deviation, respectively). At the level of low HRV, LPP latency to the CS- was significantly associated with Intrusions (β = -.47, p = .011), but this association was not found at the level of high HRV (Fig. 4 and Table 2), suggesting that safety signal processing was associated with PTSD severity only among those with poor cardiac vagal control.

Table 1
Descriptive and bivariate correlations among study variables.

	1	2	3	4	5	6	7	8	9	10
1. PCL-5 Intrusions	–									
2. PCL-5 Avoidance	.746**	–								
3. PCL-5 Negative Alterations in Cognition and Mood	.648**	.594**	–							
4. PCL-5 Alterations in Arousal and Reactivity	.594**	.468**	.846**	–						
5. P100 latency for CS+	-.233	-.232	-.191	-.145	–					
6. P100 latency for CS-	.008	-.029	-.062	-.001	.395*	–				
7. LPP latency for CS+	-.108	.090	-.117	-.068	.029	.258	–			
8. LPP latency for CS-	-.303*	-.250	-.304*	-.144	.290	.343*	.289*	–		
9. Startle for CS+	-.128	-.190	-.184	-.062	.137	-.201	-.233	.119	–	
10. Startle for CS-	.136	.138	.094	.069	-.077	-.417**	-.211	-.316*	.158	–
Mean	4.49	2.80	6.24	4.49	88.29	86.19	803.50	840.19	30.05	−4.03
SD	3.96	2.51	7.27	5.67	15.95	15.77	182.12	188.70	33.08	85.23
Minimum	0.00	0.00	0.00	0.00	75.00	75.00	600.00	600.00	1.04	−564.04
Maximum	12.00	8.00	27.00	19.00	124.00	124.00	1197.00	1189.00	178.93	43.70

Note. *$p < .05$; **$p < .01$; PCL-5 = PTSD Checklist for DSM-5; CS = conditioned stimulus; LPP = late positive potential.

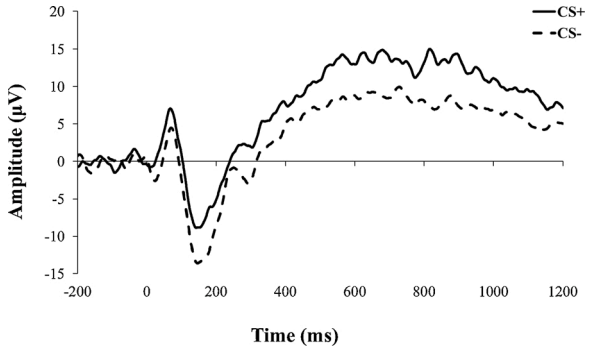
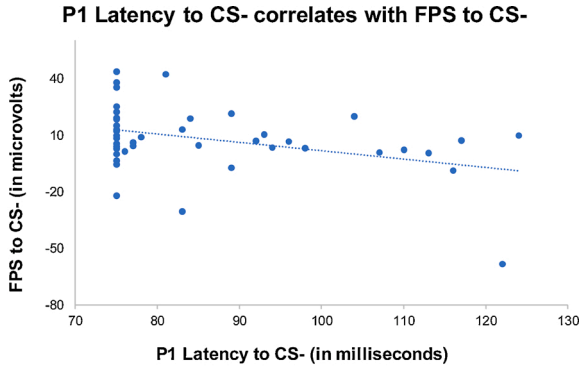


Fig. 1. LPP waveform for the CS + and CS.
Note. CS = conditioned stimulus; previously published in [17].



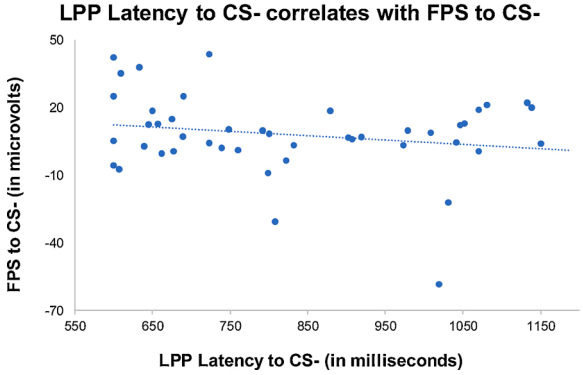
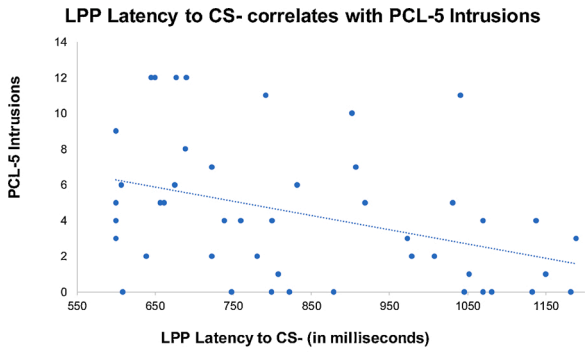


Fig. 2. Correlations between FPS and ERP Latencies for the CS.
Note. $r = -.417$, $p = .004$; FPS = fear-potentiated startle; CS = conditioned stimulus.
Note. $r = -.316$, $p = .033$; LPP = late positive potential; FPS = fear-potentiated startle; CS = conditioned stimulus.

4. Discussion

The current study probed peripheral and neurophysiological indices of safety signal learning, as well as the putative moderating role of HRV on associations between these indices and PTSD symptoms. Whereas none of the CS + analyses were significant, CS- analyses indicated that startle and ERP responses to the safety signal were associated with one another. Further, ERP responses to the safety signal were related to PTSD Intrusion symptoms, particularly among those with low HRV. Our findings suggest that ERP-based indices of safety signal learning may be useful markers of fear-based pathology and that HRV may represent a risk factor for poor safety signal learning.

While a number of studies have demonstrated that individuals with fear-based pathology exhibit exaggerated startle responses to danger signals (i.e., CS+; [5,30,1,52], a more specific phenotype is exaggerated startle to safety signals. When examining differences between healthy controls and those with fear-based disorders, prior research has indicated that heightened startle responses to the safety signal drive these findings, rather than exaggerated startle to the danger signal alone [1–4]. Our findings generally support this literature given that we only observed significant findings for the CS- and not the CS+, and they suggest that responses to safety signals may be more specific indicators of fear-related pathology. Our unexpected findings regarding longer ERP latencies for the safety signal being related to *decreased* startle suggest that longer latency of visual processing and emotional encoding for the CS- may confer better safety signal learning (i.e., fear inhibition). The most likely explanation for this finding is that our sample, while trauma-exposed, was not a clinical sample and reported low levels of PTSD symptoms. Thus, it may be more appropriate to consider our sample as a trauma-exposed control sample, which would explain the opposite effect of what has been observed in PTSD samples using other paradigms. It is also possible that in a non-clinical, relatively resilient sample, delayed 'top-down' regulation supporting safety signal learning appears as longer latencies for this visual-emotional signal processing. While this was the first study of ERP latencies for safety signals in a fear conditioning paradigm, our findings may suggest that neutral or safe stimuli elicit opposing effects in trauma-exposed individuals with versus without significant PTSD symptoms. Alternatively, increased ERP latencies could reflect greater evaluation of the safety signal prior to determining its significance, rather than delayed processing, which may be more likely in this non-clinical sample. Given that few studies that



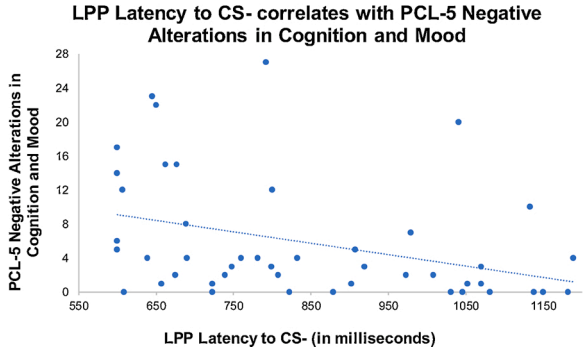


Fig. 3. Correlations between PCL-5 and LPP Latencies for the CS.
Note. r = -.303, p = .036; LPP = late positive potential; CS = conditioned stimulus;
PCL-5 = PTSD Checklist for DSM-5.
Note. r = -.304, p = .036; LPP = late positive potential; CS = conditioned stimulus;
PCL-5 = PTSD Checklist for DSM-5.

Table 2
Stepwise Regression for HRV Moderation

	β	p	SE	R^2
Step 1				
Baseline HRV	.078	.601	.615	.006
Step 2				
Baseline HRV	.104	.472	.593	
LPP latency for CS-	-.313	.035*	.003	.103
Step 3				
Baseline HRV	.122	.384	.573	
LPP latency for CS-	-.292	.041*	.003	
Baseline HRV X LPP latency for CS-	.288	.043*	.003	.185
Dependent variable: PCL-5 Intrusions				
LPP latency for CS- (simple slopes)				
Low HRV	-.474	.011*	.004	.250
High HRV	-.115	.560	.004	.250
Dependent variable: PCL-5 Intrusions				

Note. *$p < .05$; HRV = heart rate variability; LPP = late positive potential; CS = conditioned
Stimulus; PCL-5 = PTSD Checklist for DSM-5.

have specifically targeted ERP latencies as indicators of safety signal learning and the lack of other studies that specifically used fear conditioning, these results will need further replication and comparison to a clinical PTSD sample.

Another novel finding was that longer ERP latencies for the CS- were associated with significantly lower PTSD Intrusion symptoms. This is consistent with prior research demonstrating that, of all PTSD symptom clusters, the Intrusion cluster was most strongly associated with poor safety signal learning among those with PTSD [30]. The Intrusion cluster (previously called "Re-experiencing") is arguably the cluster most specific to PTSD because each symptom is directly tied to altered fear circuitry and poor fear inhibition (e.g., flashbacks, heightened emotional responding in safe situations). The unexpected direction of this finding may be understood by considering our sample as trauma-exposed controls and not a PTSD sample (discussed above). Nonetheless, our finding suggests that safety signal ERP latencies could be useful indicators of post-trauma sequalae warranting further investigation. Specifically, future research is needed to test the predictive validity of safety signal ERP latencies in assessing risk for PTSD development, as well as their utility as objective markers of treatment response.

Our finding regarding HRV suggests that ERP latencies may be particularly useful markers of safety signal learning and Intrusions among individuals with poor cardiac vagal control. It also provides further support for prior research indicating that decreased parasympathetic control indexed via HRV may be a more salient indicator for PTSD than sympathetic arousal indicated by heart rate (HR) alone. For example, Hopper and colleagues (2006) found that HR was only elevated among individuals with PTSD who had low HRV, but not those with high HRV. Thus, while exaggerated sympathetic arousal has been demonstrated in fear-based disorders (e.g., [43,45,46]), impaired parasympathetic control may be an indicator of safety signal learning (i.e., top-down inhibition) that is more specific to these populations. Further, HRV is considered a marker of emotion regulation more generally [37,38], and those with fear-based disorders such as panic and PTSD exhibit deficits in various forms of emotion regulation [39,40]. Given that the LPP has also been implicated in emotion regulation [41], studies that examine both peripheral (i.e., HRV) and neurophysiological (i.e., LPP) indices of emotion regulation are warranted to better understand safety signal learning deficits in PTSD.

In terms of study limitations, it is important to note that our sample included trauma-exposed undergraduates. Although all participants endorsed Criterion A traumatic events, their PTSD symptoms were not as severe as those of a clinical or treatment-seeking population, and their age range is lower than that of the general population. Further, only females were included in this study and therefore our findings may not generalize to male populations. We also did not assess menstrual cycle phase, time of day, or food intake, all of which may influence ERP responses [51,53,56]. Accordingly, future research is needed across sexes and accounting for variables that may affect ERPs, particularly among more severe clinical populations.

Despite these limitations. findings from the current study indicate that eye blink startle responses and ERP latencies to a safety signal are significantly associated with one another, and that safety signal ERP responses may be related to PTSD symptoms. We also demonstrated that the association between PTSD Intrusion symptoms and the LPP safety signal latency was driven by those with low but not high HRV. Collectively, these findings suggest that ERP-based indices of safety learning may have relevance for fear-related disorders and that cardiac vagal control is an important moderating factor.

Author Statement

AVS collected and analyzed the data and wrote the manuscript. ANR analyzed the data and contributed to writing the manuscript. KAP contributed to writing the manuscript. HKO supervised the study and contributed to editing the manuscript. RAP, DAP, and KJR supervised the analyses and contributed to editing the manuscript. All authors reviewed and edited the final manuscript.

Disclosures

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Otsuka Pharmaceuticals, and Takeda

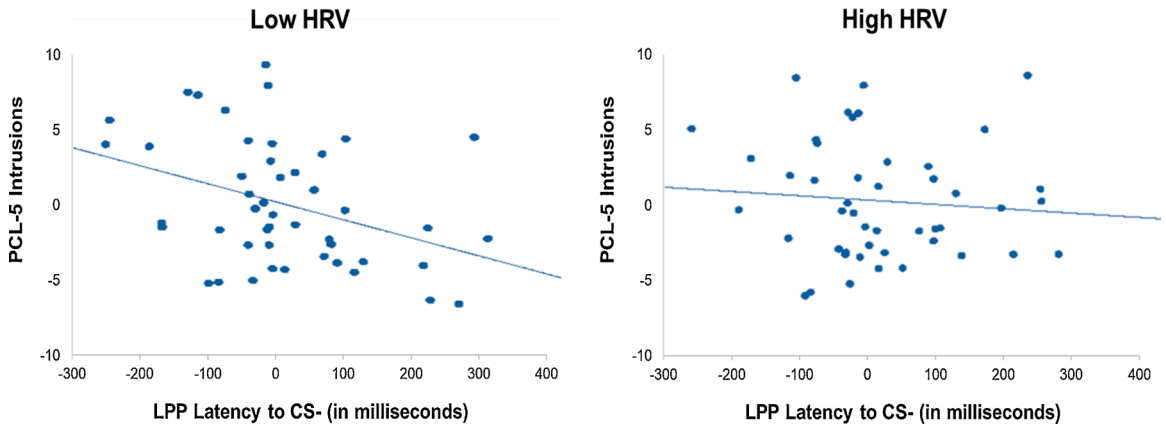


Fig. 4. PCL-5 Intrusions and LPP Latency Moderated by HRV.
Note. Residuals plotted; low HRV β = -.47, p = .011; PCL-5 = PTSD Checklist for DSM-5; HRV = heart rate variability; LPP = late positive potential; CS = conditioned stimulus.

Pharmaceuticals, one honorarium from Alkermes, and research support from NIMH, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors.

Acknowledgments

RPA (R01 MH119771) and DAP (R01 MH095809) were partially supported by funding from the National Institute of Mental Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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