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Hippocampal Threat Reactivity Interacts with Physiological Arousal to Predict PTSD Symptoms

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Abstract

Hippocampal impairments are reliably associated with post-traumatic stress disorder (PTSD); however, little research has characterized how increased threat-sensitivity may interact with arousal responses to alter hippocampal reactivity, and further how these interactions relate to the sequelae of trauma-related symptoms. In a sample of individuals recently exposed to trauma (N=116, 76 Female), we found that PTSD symptoms at 2-weeks were associated with decreased hippocampal responses to threat as assessed with functional magnetic resonance imaging (fMRI). Further, the relationship between hippocampal threat sensitivity and PTSD symptomology only emerged in individuals who showed transient, high threat-related arousal, as assayed by an independently collected measure of Fear Potentiated Startle. Collectively, our finding suggests that development of PTSD is associated with threat-related decreases in hippocampal function, due to increases in fear-potentiated arousal.

Significance Statement

Alterations in hippocampal function linked to threat-related arousal are reliably associated with post-traumatic stress disorder (PTSD); however, how these alterations relate to the sequelae of trauma-related symptoms is unknown. Prior models based on non-trauma samples suggest that arousal may impact hippocampal neurophysiology leading to maladaptive behavior. Here we show that decreased hippocampal threat sensitivity interacts with fear-potentiated startle to predict PTSD symptoms. Specifically, individuals with high fear-potentiated startle and low, transient hippocampal threat sensitivity showed the greatest PTSD symptomology. These findings bridge literatures of threat-related arousal and hippocampal function to better understand PTSD risk.

Introduction

Threat is known to alter hippocampal function, a region critically implicated in supporting memory (Eichenbaum, 2001). Whereas moderate threat increases hippocampal sensitivity (Joëls et al., 2006), excessive threat impairs hippocampal function (Kim & Diamond, 2002; McEven, 2007; Henckens et al., 2009; Schwabe & Wolf, 2012; Bisby & Burgess, 2013, 2017). In PTSD, decreased hippocampal engagement propagates traumatic memories (Hayes et al., 2011) and impairs discrimination between danger and safety signals, leading to the overgeneralization of fear (Besnard & Sahay, 2016; Asok et al., 2019), which underlies PTSD (e.g., Hayes et al., 2011). Further, lower hippocampal engagement during inhibitory tasks has been associated with PTSD (van Rooij et al., 2016; van Rooij, 2018). However, contradictory evidence shows increased hippocampal engagement during trauma-related memory and imagery in individuals with PTSD (Bremner et al., 2003; Tural et al, 2018). These inconsistencies may result from the functional demands placed on the hippocampus (threat versus safety detection) and the neuromodulatory profile in which these demands occur (high versus low arousal). Here, we characterize the relationship amongst hippocampal function, threat-related arousal, and PTSD symptomology in a large sample of trauma-exposed individuals.

We previously developed a model of how threat-related arousal alters hippocampal function, biasing information processing away from hippocampus (HPC) to other learning structures due to arousal-mediated norepinephrine (NE) engagement (Murty & Adcock, 2017; Clewett & Murty, 2019). Specifically, we predict that threat-related arousal disrupts behavioral and neural indices of hippocampal function. Thus, this model posits that an individual's threat sensitivity, including heightened defensive arousal, can determine downstream impairments in hippocampal function and associated symptoms (Murty & Adcock, 2017).

Many aspects of PTSD fall within this theoretical framework. Threat-predictive behaviors —such as fear-potentiated startle (FPS) responses to danger and safety cues are heightened in PTSD (Grillon & Morgan, 1999; Grillon & Baas, 2003; Glover et al., 2011; Norrholm & Jovanovic, 2018), and are associated with increased NE engagement (Yehuda et al., 1996). Patients with PTSD 1) show greater arousal in response to cues of both danger and safety (Jovanovic et al., 2010; Shin & Liberzon, 2010; Jovanovic et. al., 2012; Pitman et al., 2012; Briscione et al., 2014); 2) fail to inhibit fear responses during fear extinction (Milad et al., 2009; Jovanovic et al., 2010; Jovanovic et al., 2012; Maren & Holmes, 2016; Cacciaglia et. al., 2017; Maeng & Milad, 2017); and 3) over-generalize fear responses (Hoffmann et al., 2014). Yet these profiles of threat sensitivity have yet to be directly related to hippocampal function. However, our model predicts these increases in arousal may divert information processing resources away from the hippocampus, leading to PTSD risk.

In the current study, we extend our model to trauma-related behavioral impairment by characterizing hippocampal dysfunction in relation to heightened arousal and PTSD symptom severity in trauma-exposed participants. We operationalize hippocampal threat sensitivity as responses to fearful versus neutral face stimuli with functional imaging, and arousal as FPS responses to learned danger and safety cues. We also make a distinction between the anterior (aHPC) and posterior (pHPC) portions of the hippocampus, given aHPC is reportedly more responsive during fear learning and trauma-related arousal (Bannerman et al., 2004; Dolcos et al., 2004; Murty et al., 2010; Strange et al., 2014; Hayes et. al., 2011; Abdallah et al., 2017). Our main analyses characterize transient HPC responses reflecting initial threat sensitivity in this region, but we also conduct exploratory analyses reflecting more sustained activity indicating contextual processing. We hypothesized that 1) reductions in hippocampus (HPC) threat

sensitivity, specifically the aHPC, will predict PTSD symptom severity in trauma-exposed individuals and 2) associations between HPC-threat sensitivity and PTSD symptoms will be mediated by FPS responses.

Methods

Participants

Participants were recruited from United States emergency departments (EDs) as part of a multisite longitudinal study: Advancing Understanding of RecOvery afteR traumA (AURORA) (U01MH110925, McLean et al., 2020). Twenty-two EDs within the Northeast, Southern, mid-Atlantic, or Midwest regions of the United States enrolled patients in the ED within 72 hours of trauma exposure. All participants were ages 18-75, able to speak and read English, oriented in time and place, physically able to use a smartphone, and possessed a smart phone for >1 year. Potential participants were excluded if they had a solid organ injury >grade 1, significant hemorrhage, required a chest tube or general anesthesia, or were likely to be admitted for >72 hours. MRI scans were collected between two-to-three-weeks later (M_{day}=18, SD_{day}=6, referred to as two-week assessment from here on) at a laboratory visit which included MRI and psychophysiology at four hub sites: McLean Hospital, Emory University, Temple University, or Wayne State University. All participants gave written informed consent as approved by each study site's Institutional Review Board.

Data collection for the parent study is ongoing and released in specific data freezes. For the second large deep-phenotyping freeze of 202 participants, we focused analyses on utilizing fMRI data during an emotional face processing task and startle data in a fear conditioning

paradigm to predict concurrent and future PTSD symptoms (see Figure 1 for the timeline of assessments). One hundred and sixteen participants (Age: M = 35.19, SD = 12.51 years, 76 Female) were included after excluding for missing PTSD data, and fMRI preprocessing (see fMRI Preprocessing below) in the release. Participant demographics and psychometric averages are reported in Table 1.

Psychometric Assessments

PTSD symptoms were assessed using the PTSD Symptom Checklist for DSM-5 (PCL-5). The PCL-5 is a 20 item self-report questionnaire assessing the presence and severity of various post-traumatic stress symptoms (Weathers et al., 2013). Participants rated symptoms on a scale of 0 (not at all) to 4 (extremely) for the severity of each symptom. A raw total score was computed from summing the individual items and converted to a T-score, reflecting a more general score. Our main analyses focused on the symptom severity at 2-weeks. In an exploratory analysis, we also tested how PTSD symptoms changed from 2-weeks to 8-weeks, and to 3-months after trauma exposure (Figure 1).

Acquisition and Analysis of Fear-Potentiated Startle (FPS)

Fear conditioning was assessed with a fear-potentiated startle experimental paradigm used successfully in adult trauma populations (Glover et al., 2011; Norrholm et al., 2011). Participants completed this task during the laboratory visit for the MRI scans within the two weeks of their trauma exposure (Figure 1). Participants were seated approximately 3 feet from a computer screen and asked to remain still and watch the monitor. The protocol consisted of a habituation, acquisition, and extinction phase, all on the same day, lasting a total of 45-60 minutes. The

habituation phase included four trials of each type: startle noise alone (NA), a conditioned stimulus (CS) which would be paired with the unconditioned stimulus (US) during acquisition (CS+), and a CS which would not be reinforced during acquisition (CS-). The acquisition phase followed habituation and contained 3 blocks with 12 trials each (36 total acquisition trials). The US was an aversive 250-ms air blast with an intensity of 140 p.s.i directed at the larynx. Both CSs were colored shapes presented on the monitor in front of the participant using Superlab presentation software (Cedrus, Inc.) for 6 seconds prior to the startle probe. The CS+ co-terminated with the US 0.5 seconds after the presentation of the startle stimulus. The shape and color of the CS- and CS+ were counterbalanced across subjects. The CS+ was reinforced with the air blast on 100% of the acquisition trials. The air blast was emitted by a compressed air tank attached to polyethylene tubing and controlled by a solenoid switch. This US has been used in several of our previous studies and consistently produces robust fear-potentiated startle (Jovanovic, 2005; Norrholm et al., 2011). The extinction phase occurred 10 minutes after acquisition and consisted of four blocks of four trials each, NA, CS+, CS-, for a total of 16 trials of each type. During extinction, the CS+ was no longer paired with the air blast. In all phases, the inter-trial intervals were randomized to be 9 to 22 sec in duration.

The acoustic startle response data were acquired using the electromyography (EMG) Bionomadix module of the Biopac MP160 for Windows (Biopac Systems, Inc., Aero Camino, CA). Participants were screened for hearing impairment with an audiometer, (Grason-Stadler, Model GS1710), and were required to hear tones ranging from 250 Hz to 4000 Hz above 30dB. The eyeblink component of the acoustic startle response was measured by EMG recordings of the right *orbicularis oculi* muscle with two 5-mm Ag/AgCl electrodes. One electrode was positioned 1 cm below the pupil of the right eye and the other was placed 1 cm below the lateral

canthus. Impedance levels were less than 6 kilo-ohms for each participant. The startle probe was a 108-dB [A] SPL, 40-ms burst of broadband noise, delivered binaurally through headphones.

EMG data were sampled at 1000 Hz and the acquired data were filtered with low- and high-frequency cutoffs at 28 and 500 Hz in MindWare software (MindWare Technologies, Inc.) and exported for statistical analyses. The maximum amplitude of the eyeblink muscle contraction 20-200 ms after presentation of the startle probe was used as a measure of the acoustic startle response. Fear-potentiated startle (FPS) was calculated as a percent potentiation: First, a difference score is calculated by subtracting average startle magnitude to the NA trials from average startle magnitude to the CS+ (danger signal) and CS- (safety signal). The difference score was then divided by the startle magnitude to NA trials, and finally multiplied by 100. Percent potentiation scores were used because they have been shown to take into account the variability in individual animals (Walker and Davis, 2002). We also calculated an FPS difference score by subtracting FPS to CS- from FPS to CS+, highlighting participants' ability to discriminate between danger and safety.

MRI data acquisition

Prior to scanning, participants were screened for MR contraindications or other exclusion criteria. Female participants and participants who were potentially childbearing completed a pregnancy test prior to entering the MR environment. MRI scans were completed on 3T Siemens scanners at each site. Scan sequences were largely harmonized between imaging sites with some variability in sequence parameters due to hardware differences (see Table 2 for overview of all imaging parameters). Following familiarization with the MR environment, participants completed first the T1-weighted anatomical imaging, and then the functional MRI (fMRI). T1-

weighted images were used for co-registration (see Preprocessing below). Below we report on the passive viewing of fearful faces during fMRI scan (see McLean et al., (2020) for the details of all MRI scans not reported here).

fMRI Task Design

Integral to the assessment of neural circuitry related to PTSD in the peri-and-post traumatic periods is the inclusion of stimuli and tasks to probe various cognitive and affective processes. Three separate tasks were chosen for the AURORA study; the neural substrates activated within each task have been highly replicated and are in line with the NIH Research Domain Criteria (RDoC) constructs (Insel et al., 2010). Participants completed passive viewing of fearful faces (Stevens et al., 2013), a go/no-go task (Jovanovic et al., 2013), and a card-guessing (reward) task (Delgado et al., 2000).

We report on the fearful face processing task (Stevens et al., 2013). This task has been used in several PTSD studies and has consistently demonstrated greater activation of the amygdala to fearful, compared to neutral, faces (Shin et al., 2005; Stevens et al., 2013; Kim et al., 2019). Participants viewed alternating blocks of either neutral or fearful faces of Caucasian race from the Ekman and Friesen faces library (Ekman and Friesen, 1976). Prior to the task participants were told that they will be shown a series of faces and instructed to "be alert and pay attention to the faces". Blocks of fearful and neutral stimuli were sequentially presented with the order of fearful and neutral blocks counterbalanced across participants (15 blocks each). In each block, a total of eight faces (four male, four female) were presented for 500ms each with a 500ms fixation cross presented after each face. Every 10^{th} block, participants received a

10000ms fixation cross as a "rest period" and instructed to "relax and look at the screen" (Kim et al., 2019). No behavioral responses were collected from participants during this task to minimize artifacts due to other neural processes not related to processing the visual stimulus.

MRI data conversion and quality control

DICOM images were converted to NIFTI format with Brain Imaging Data Structure (BIDS) nomenclature using dcm2niix (Li et al. 2016) and were visually inspected for conversion errors and data exclusion criteria (e.g., signal drop-out from Falx calcification, anatomical abnormalities). Further quality control was achieved by running the MRIQC pipeline (version 0.10.4 in a Docker container) (Esteban et al. 2017) on the structural and functional images.

fMRI Preprocessing

FMRI preprocessing was performed with FSL 6.0.1. (Jenkinson et al., 2012). First, the T1-weighted (T1w) anatomical image was skull stripped using the Brain Extraction Tool (BET). This image was used to assist in spatial normalization processes detailed below. Brain tissue segmentation of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) was performed on the brain extracted T1w images using FAST. These segmentations were used to extract time series from the wm and csf for reduction of noise in our preprocessing stream. FMRI preprocessing was completed using the fMRI Expert Analysis Tool (FEAT) version as implemented in FSL 6.0.1. using a pipeline designed to minimize the effects of head motion (Murty et al., 2018). This included simultaneous head motion correction, and non-linear warping to the MNI space, but no temporal or spatial filtering.

Following preprocessing, we ran a general linear model (GLM), where the onset of fearful and neutral blocks of faces were modeled as separate regressors, and were convolved with a double-gamma hemodynamic response function as an event-related response capturing the block onset. Six head-motion parameters, and their first derivatives, and time series extracted from cerebrospinal fluid and white matter were added as covariates to the model to reduce noise. For our exploratory analysis of sustained responses, a second GLM was run with the additional regressors to model the entire duration (8s) for the fearful and neutral blocks in addition to the transient on-set block, i.e., to model the sustained activity. The GLMs were run using FEAT version 6.0 as implemented in FSL 6.0.3. First level contrasts of fearful>baseline, neutral>baseline, and fearful>neutral contrasts were estimated in our regions-of-interest (ROIs), separately for each hemisphere.

Defining Regions of Interest

For all of our analyses we focused on the hippocampus as our priori region of interest. The hippocampus was identified in standard space with a probabilistic atlas thresholded at 50% from the Harvard-Oxford probabilistic subcortical atlas as implemented by FSL (Desikan et al., 2006; https://neurovault.org/collections/262/). We then divided the original hippocampus along its long axis into three tertiles and used the anterior and posterior tertiles as our anterior and posterior hippocampus ROIs (Murty et al., 2016). We did not use the middle tertile in this analysis as signals from this region have been shown to be a mixture of anterior versus posterior hippocampal processing (Kerr et al, 2007; Poppenk et al., 2013). For each participant, all ROIs were transformed into subject-specific space using the inverse of the parameters estimated during normalization. Individual ROIs were created in the subject-specific for both anatomical and

functional spaces. In cases where ROIs in the subject-space had overlapping voxels such voxels were included in the ROIs in which they had the highest probability of inclusion. Each ROI was manually inspected by a trained research assistant.

Data Analysis

We first resampled all of the preprocessed functional data and anatomical ROIs into 2.0 mm isotropic voxels in MNI space. For the univariate analyses, we extracted the event-specific mean activity in all our ROIs for the task phase, acquiring z scores for the following contrasts: 1) activity when a fearful face was viewed was compared to the baseline at task phase (fearful>baseline), 2) activity when a neutral face was viewed was compared to the baseline at task phase (neutral>baseline), and finally, 3) activity when a fearful face was viewed was compared to the activity when a neutral face was viewed (fearful>neutral). All analyses were completed for the right and left hemispheres separately.

Secondarily, we tested the effect of emotion on the activity of the left anterior, right anterior, left posterior, and right posterior hippocampus in four separate models. Then, we assessed if fear-related activity (fearful>neutral) predicted the participants' PTSD symptom severity at 2 weeks. To do so, we tested four separate models where the 2-weeks PTSD symptoms were predicted by the activity in left anterior HPC, right anterior HPC, left posterior HPC, and right posterior HPC. Across all four models, significance was set at $p < 0.05$ (uncorrected), while Bonferroni corrections for multiple comparisons were set at $p < 0.0125$. Importantly, we tested two additional models, which included activity from both left and right hemispheres as covariates (separately for anterior and posterior HPC). Then for each subregion, we tested whether the coefficients differed between left and right to test any effects of laterality.

Next, we tested whether threat-related activity in the hippocampus relates to arousal responses. Twenty-two subjects were removed from these models because of missing startle data (N=95, 62 Female). We first tested whether the fear acquisition elicited the intended effects, comparing participants' fear-potentiated startle responses to CS+ (danger signal) and CS- stimuli (safety signal). Next, we tested whether fear-potentiated startle is predicted by the threat-related activity in the hippocampus. Finally, we tested whether startle responses interacted with fear-related hippocampal reactivity in predicting the PTSD symptoms at two-weeks post-trauma. Importantly, we tested this assumption only in the regions whose activity yielded significant effects on the PTSD symptoms at 2-weeks (see Results section for more details). Therefore, we tested a total of two models here, with significance set at $p < 0.05$ (uncorrected) and Bonferroni correction set at $p < 0.025$.

We next tested a time-based hypothesis that hippocampal threat sensitivity, together with physiological threat sensitivity would predict PTSD symptom change across the follow-up assessments (eight-weeks and three-months post trauma). To that end, we first tested a mixed-effects model with a two-way interaction between threat-related activity and time (2-weeks, 8-weeks, and 3-months), separately in anterior and posterior hippocampus. We then tested a second mixed-effects model with a three-way interaction model between threat-related hippocampal activity, fear-potentiated startle responses and time, separately in anterior and posterior sub-regions. Across all four models, significance was set at $p < 0.05$ (uncorrected), while Bonferroni corrections for multiple comparisons were set at $p < 0.0125$.

We next conducted an exploratory analysis. Specifically, we tested whether the sustained hippocampal activity related to PTSD symptomatology differently than transient activity. To that end, we repeated the analyses above using the activity extracted from the fearful > neutral

427 contrast from the GLM where sustained activity was modeled. Therefore, we tested four initial
428 models where PTSD symptoms at two-weeks were predicted by the sustained hippocampus
429 activity. The significance was set at $p < 0.05$ (uncorrected) and Bonferroni correction set at $p <$
430 0.0125 for these models. For the regions with significant effects on PTSD outcome that survived
431 the Bonferroni correction, we then proceeded with the additional tests with the interaction
432 models (FPS difference by hippocampal activity). This resulted in two additional tests, for which
433 the significance set at $p < 0.05$ (uncorrected) and Bonferroni correction set at $p < 0.025$.
434 The unstandardized beta coefficients are reported for all our significant results. All
435 analyses were performed using R software (R package version 3.4.1) using the anova (the stats
436 library), glm (the stats library), glmer (the lme4 library), linearHypothesis (the car library), and
437 simple_slopes (the reghelper library) functions depending on the test. Finally, regression models
438 predicting PTSD symptoms were tested using a Poisson distribution (family = Poisson (link=
439 "log")) since the symptom distribution was positively skewed. Age, gender and scanner type (to
440 control potential effects of different scanners on the hippocampal signal) were added in all of the
441 models as covariates. Finally, all continuous variables were standardized before testing the
442 regression models. Analysis scripts are available upon request.
443

Results

Hippocampus does not differentiate between fearful and neutral faces

Four separate one-way ANOVAs testing the effect of emotion (fearful, neutral) on the neural activity were run in the left anterior, right anterior, left posterior and right posterior hippocampus. The models did not reveal any significant main effect of emotion (left anterior: $F(2, 230) = 0.01$, $p = 0.8$; right anterior: $F(2, 230) = 0.001$, $p = 0.9$; left anterior: $F(2, 230) = 1.2$, $p = 0.3$; right anterior: $F(2, 230) = 0.06$, $p = 0.8$), suggesting that hippocampus does not differentiate between fearful and neutral faces.

Decreased transient left hippocampal fear-related activity predicts PTSD symptoms

Threat-related transient activity in left anterior (left: $\beta = -0.08$, $SE = 0.02$, $p < 0.0001$) and left posterior hippocampus ($\beta = -0.09$, $SE = 0.02$, $p < 0.0001$) was associated with PTSD symptom severity at 2-weeks (see Figure 2 and Table 3), such that relatively less threat-related reactivity in the hippocampus the greater their 2-week PTSD symptom. All of the reported models with a significant effect survived Bonferroni correction ($p_{adjusted} = 0.0125$). However, right hippocampus was not a significant predictor of PTSD symptoms at 2-weeks (anterior: $p = 0.22$; posterior: $p = 0.05$), thus we did not test the following FPS-related models in right anterior and posterior hippocampus.

It is important to note that left anterior and left posterior hippocampus activity were correlated ($r(114) = 0.21$, $p = 0.03$); however the low correlation between the two subregions emphasize the relative orthogonality of the anterior and posterior hippocampus activity in predicting PTSD symptom severity. Finally, comparing coefficients from left and right hemisphere for both hippocampal subregions revealed that the association between hippocampal

activity and PTSD symptom severity was stronger in the left than right hemisphere (anterior: $X^2(109) = 10.69$, $p = 0.001$; posterior: $X^2(109) = 13.4$, $p = 0.0003$).

Increased Fear-Potentiated Startle (FPS) responses during fear acquisition predict PTSD symptoms

Participants had greater fear-potentiated startle (FPS) response to the CS+ (danger) compared to the CS- (safety) during fear acquisition ($t(93) = 3.4$, $p = 0.001$), suggesting that they learned to discriminate between the danger and safety cues. Therefore, we focused on the FPS difference between danger and safety cues as our main predictor in the startle models. To that end, we first tested whether FPS difference was associated with the PTSD symptoms at two weeks. The results revealed that increased FPS difference was associated with higher PTSD symptoms ($\beta = 0.07$, $SE = 0.02$, $p = 0.0002$).

Fear-related transient activity in the hippocampus and startle responses during fear acquisition interactions predict PTSD symptoms

The models testing whether threat-related activity in the hippocampus was associated with fear-potentiated startle responses did not reveal any significant relationship (left anterior: $F(3,90) = 0.7$, $p = 0.6$ & left posterior: $F(3,90) = 0.5$, $p = 0.7$). Critically, we found that significant interactions between transient threat-related hippocampal activity and FPS difference predicted 2-week PTSD symptoms (left anterior: $\beta = -0.04$, $SE = 0.02$, $p = 0.017$; left posterior: $\beta = -0.09$, $SE = 0.03$, $p = 0.001$). Results from both left anterior and left posterior hippocampus survived Bonferroni corrections ($p_{adjusted} = 0.025$). To determine if these findings generalized to alternative approaches to estimating FPS, we separately calculated FPS by utilizing a

residualization approach (i.e., using the residual FPS to CS+ and CS- after regressing out the average startle magnitude to the NA trials). This approach yielded results similar to hippocampus*FPS interactions in the posterior, but not anterior, hippocampus (anterior: β =: 0.007, p = 0.63; posterior: β =: 0.08, p = 0.004), which suggests that the reported FPS-related PTSD outcomes in the posterior hippocampus are specific to threat-related arousal instead of individual differences in baseline startle responses.

Simple slopes analyses revealed that the inverse relationship between transient left anterior hippocampal threat reactivity and PTSD symptoms at two weeks was stronger for high (+1 SD) FPS differentiation (β = -0.07, SE = 0.03, t = -2.8, p = 0.005). Moreover, the relationship between transient left posterior hippocampal threat reactivity and PTSD symptoms was stronger for both mean and high (+1 SD) FPS differentiation: (mean: β = -0.06, SE = 0.02, t = -2.82, p = 0.005; high: β = 0.15, SE = 0.04, t = -3.99, p < 0.0001) (Figure 3). These effects suggest that individuals with higher FPS differentiation and lower transient hippocampal reactivity to threat report higher PTSD symptoms.

Independent Contributions of Fearful and Neutral Hippocampal Reactivity to PTSD symptoms

To better decompose the component effects guiding the relationships above, we next tested whether our hippocampal effects were driven by changes in the hippocampus activity specific to the fearful (fearful>baseline) or neutral (neutral>baseline) faces. The fearful-only analyses revealed that decreased transient reactivity in left anterior and posterior hippocampus was associated with greater PTSD symptoms at two weeks (anterior: β = -0.06, SE = 0.02, p < 0.0004; posterior: β = -0.04, SE = 0.02, p = 0.015, both effects survive Bonferroni adjustments at

513 $p_{adjusted}$ = 0.025). However, there were no significant interactions between the transient fearful-
514 only hippocampal activity and FPS difference in predicting PTSD symptoms at two-weeks.
515 On the other hand, increased transient neutral-only activity in left posterior hippocampus
516 was associated with increased PTSD symptoms at two-weeks (β = 0.04, SE = 0.02, p = 0.038,
517 albeit it did not survive Bonferroni corrections at p = 0.025). Importantly, the neutral-only
518 activity in left posterior hippocampus significantly interacted with FPS difference score in
519 predicting PTSD symptoms at two-weeks (β = 0.06, SE = 0.03, p = 0.02). Simple slopes analysis
520 revealed that this association was significant at the lower end of the FPS difference (-1 SD, p =
521 0.045) and at the moderate (mean; p = 0.003) and higher (+1 SD; p < 0.0001) left posterior
522 hippocampal activity to neutral faces. These results suggest that decreased transient activity to
523 fearful stimuli and increased transient activity to neutral stimuli in hippocampus both contribute
524 to increased PTSD symptomatology.
525
526 *PTSD Symptom Change Across Time*
527 We took a growth modeling approach to analyze whether the symptom change from 2-
528 weeks to 8-weeks and 3-months follow-ups is predicted by hippocampal threat reactivity and/or
529 FPS differentiation. For these analyses, we focused on the left anterior and left posterior
530 hippocampus given their significant role in two-week PTSD outcomes. Analyses revealed a main
531 effect of time (Table 4), such that PTSD symptoms decreased from 2-weeks to 8-weeks and 2-
532 weeks to 3-months follow-up assessments. However, there was no significant interactions
533 between time, hippocampal threat reactivity, and FPS differentiation (Table 4).
534
535 *Age, Gender and Scanner Effects on PTSD*

Age, gender and scanner type were included as covariates in all models. In all the 2-weeks PTSD models reported above, gender was a significant predictor of PTSD symptoms (Table 3) such that female subjects reported higher PTSD symptom score compared to male participants. Age was also a significant predictor of PTSD symptoms in the simple 2-weeks models, but this effect was no longer evident when the FPS difference was added to the models as an interaction term (Table 3). Finally, including the scanner type as a covariate ensured that the reported significant hippocampal effects were not influenced by the scanner related differences across the study sites.

Sustained fear-related activity in the hippocampus predicts increased PTSD symptoms

In a set of exploratory analyses, we next tested whether sustained fear-related hippocampal activity relates to PTSD symptoms differently than the transient activity. Notably, these analyses included both sustained and transient activity within the same fMRI model when estimating single-subject parameters, highlighting independent contributions of sustained activity. The results revealed that increased sustained fear-related activity in left and right posterior (left: $\beta = 0.05$, $SE = 0.02$, $t = 2.69$, $p = 0.007$; right: $\beta = 0.06$, $SE = 0.02$, $t = 3.17$, $p = 0.002$) hippocampus was associated with increased PTSD symptoms at two-weeks (Figure 4A and 4B). These results suggest that sustained posterior hippocampal reactivity to fear-related information relates to higher PTSD symptomatology (Table 5). Importantly, interactions between the sustained posterior hippocampus and FPS difference significantly predicted PTSD symptoms at two-weeks (left: $\beta = 0.04$, $SE = 0.02$, $t = 2.27$, $p = 0.024$; right: $\beta = 0.04$, $SE = 0.02$, $t = 2.45$, $p = 0.015$, both effects survive Bonferroni corrections at $p_{adjusted} = 0.025$) (Figure 4C and 4D). Simple slopes analyses revealed that this interaction effect was stronger at the higher levels of

559 FPS difference (+1 SD: $p = 0.0007$ in left posterior; $p < 0.0001$ in right posterior). Moreover, the
560 interaction effects were also stronger for the moderate (mean: $p < 0.0001$ in left posterior; $p <$
561 0.0001 in right posterior) and higher levels of sustained posterior hippocampus activity (+1 SD:
562 $p < 0.0001$ in left posterior; $p < 0.0001$ in right posterior). Accordingly, individuals with higher
563 sustained fear-related activity in posterior hippocampus and higher FPS difference report higher
564 PTSD symptoms at two weeks.
565

566 **Discussion**

567 Heightened arousal due to threatening events alter hippocampal activity (Kim &
568 Diamond, 2002; Henckens et al., 2009; Schwabe & Wolf, 2012; Bisby & Burgess, 2013, 2017),
569 which has been suggested to strengthen traumatic memories and exacerbate symptoms (Hayes et
570 al., 2011). Here, we assessed the relationship between threat sensitivity, hippocampal function,
571 and PTSD symptomology in a group of individuals recently exposed to trauma (McLean et al.,
572 2020).

573 We first showed that decreased transient hippocampal threat sensitivity was related to
574 PTSD symptom severity at two-weeks after trauma exposure. Specifically, we found that
575 participants who showed reduced transient threat reactivity in left anterior and left posterior
576 hippocampus reported more severe PTSD symptoms. This is consistent with previous research
577 that showed reduced left hippocampus activity in PTSD patients when remembering trauma-
578 related memories (Bremner 2001; Bremner et al., 2003; Hayes et al., 2011) or recently learned
579 negative information (Bisby et al., 2017). Relatedly, reduced hippocampal activation during a
580 response inhibition task has also been associated with increased PTSD symptoms in chronically
581 traumatized individuals (van Rooij et al., 2016; van Rooij & Jovanovic, 2019), and predicted
582 future PTSD symptoms in recently traumatized civilians (van Rooij et al., 2018). Together with
583 these earlier findings, our study supports an account of intact hippocampal function playing a
584 role in trauma resilience (van Rooij et al., 2021).

585 An important distinction between our findings and the previous research, however, is that
586 previous research has shown that the association between the hippocampal dysfunction and
587 PTSD was driven by the anterior portion of the hippocampus (Hayes et al., 2011; Dickie et al.,
588 2011; Abdallah et al., 2017), a region that is often implicated in fear learning (Kjerstrup et al.,

589 2002; Bannerman et al., 2004; Murty et al., 2010; Strange et al., 2014). However, we did not find
590 a functional distinction between anterior and posterior portions of the hippocampus in predicting
591 PTSD symptom severity, and our posterior hippocampus results were more robust to
592 characterizing interactions with FPS in predicting PTSD symptoms. Moreover, albeit low, the
593 activity in anterior and posterior hippocampus were correlated in the current sample. Therefore,
594 our results are more in line with the results of Lazarov and colleagues (2017), who recently
595 showed that the functional distinction between anterior and posterior hippocampus in their
596 connectivity to regions in the default mode network, e.g., ventromedial prefrontal cortex,
597 precuneus and posterior cingulate cortex, which are often implicated in PTSD patients, is
598 eliminated in individuals with PTSD but not in trauma exposed controls.

599 Our findings suggest a complex role of the hippocampus in threat sensitivity since it is
600 highly sensitive to threatening stimuli after traumatic experiences. This heightened hippocampal
601 sensitivity protects the individual from developing severe symptoms of PTSD, but only to the
602 extent that it can process the negative information. We found that the relationship between
603 hippocampal threat reactivity and PTSD symptom severity is modulated impaired ability to
604 differentiate threat from safety (CS-). Specifically, our data demonstrated greater threat
605 anticipation, as evidenced by the greater differentiation between fear-potentiated startle
606 responses to CS+ and to CS-, was associated with lower reactivity in the left hippocampus.
607 Moreover, this interaction between the reduced hippocampal reactivity and greater threat
608 anticipation was linked with PTSD symptom severity at two-weeks post-trauma. Although
609 previous research has established an association between reduced hippocampal activity and
610 arousal symptoms of PTSD (Hayes et al., 2011), and between an impairment in delineating
611 danger and safety cues and the development of PTSD (Jovanovic et al., 2010; Shin & Liberzon,

2010; Pitman et al., 2012; Jovanovic et al., 2012; Briscione et al., 2014; Maeng & Milad, 2017), our results are unique in demonstrating that the same individuals who are highly reactive to threat cues also show impaired hippocampal engagement in the processing of threat cues, which is associated with PTSD symptom severity.

These findings may be surprising in the context of the prior PTSD literature, but our results are consistent with our recent model detailing arousal-related impairments in hippocampal function. Our model suggested that threat-related arousal impairs hippocampal function, biasing information processing away from the hippocampus to other learning structures, particularly when arousal-mediated systems such as the NE system are engaged (Clewett & Murty, 2019). Critically, PTSD studies have shown increased norepinephrine release in response to stress (see Bremner, 2006 for a review), which may bias hippocampal threat reactivity. Given this evidence, we conclude physiological arousal, a putative marker of the NE system, represents an important individual difference measure predicting whether the hippocampus will propagate or mitigate PTSD symptoms.

In a set of exploratory analyses, we also explored the relationship of more sustained hippocampal responses to threat and how they relate to PTSD symptoms. Specifically, we found unlike transient threat processing in the hippocampus, increased sustained engagement of the hippocampus in response to threatening stimuli positively predicted PTSD symptoms. These effects were even more pronounced in individuals who showed greater differentiation between threat and safety cues as measured by FPS. The opposing directions of these sustained responses compared to transient responses suggest that differential mechanisms may be at play when considering fast, event-evoked responses and more prolonged, sustained responses. Critically, the hippocampus has been shown to subserve multiple roles, including subserving the formation

and retrieval of episodic memories (Eichenbaum, 2001), but also regulating stress responses that underlie hyper-salience and defensive behaviors (Herman et al., 2016; Jimenez et al., 2018; Goldfarb et. al., 2020). While highly speculative, we suggest that the more transient responses in the hippocampus reflects more adaptive forms of memory encoding that can protect individuals from developing PTSD symptoms, whereas the more sustained responses may reflect sustained signals that propagate HPA-axis engagement leading to greater susceptibility to the damaging effects of trauma. However, more empirical work that includes explicit, dynamic measures of episodic memory formation and hyper-salience are needed to confirm these hypotheses.

The current study had a few features that limited our ability to fully interpret our findings, that should be addressed in future work. First, our fearful face processing task did not include dynamic assays of behavior—such as eye-tracking, subsequent memory, or physiological arousal—to help us integrate our neural findings with behavioral outcomes. Including more behavioral variables related to real-time assessments of hippocampal threat sensitivity could provide clear relationships to PTSD symptoms. Second, all participants in our study were exposed to trauma in recent history. Thus, our study lacks the baseline of a normative, non-trauma exposed cohort, which could help us determine if individuals with low PTSD reflect signals of resilience and/or compensation. Third, our current sample of trauma participants consisted mainly of individuals in recent automobile accidents, with relatively low sampling of other forms of trauma. Thus, the current data set was unable to disambiguate how different forms of trauma relate to PTSD symptoms, which has important implications for the development of tailored therapeutics.

Together, our findings are consistent with a novel model of the involvement of the hippocampus in mediating PTSD symptomology. Specifically, we propose that decreased threat-

sensitivity in the hippocampus, a structure known to support safety learning, contributes to both concurrent PTSD symptoms as well as the propagation of these symptoms into the future. However, our model further specifies that an important mediator of this relationship is state-dependent physiological arousal. Thus, physiological arousal may divert information processing away from the hippocampus during threat learning yielding vulnerability and risk. Future studies are warranted linking engagement of the hippocampal system to memory fragmentation and threat-related memory, as prior work has specified this relationship in normative populations.

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Figure 1. Experimental Timeline. Participants were recruited from emergency departments after exposure to trauma. Trauma symptoms were assessed two-weeks, eight-weeks and three-months post-trauma using PCL-5. As part of the two-weeks assessments, participants also completed a fear conditioning task, and a face viewing task in the MRI scanner. During fear conditioning, colored shapes were either reinforced (CS+) or not-reinforced (CS-) with air blast, and fear-potentiated startle responses (FPS) to the CS+ and CS- stimuli were measured. In the functional MRI (fMRI) study, participants passively viewed fearful and neutral faces in the scanner. CS: Conditioned Stimulus; ED: Emergency Department; FPS: Fear-Potentiated Startle; PCL-5: PTSD Symptom Checklist for DSM-5.

Figure 2. Reduced threat-related transient activity in hippocampus predicts PTSD severity. Increased threat-related transient activity in left anterior and left posterior HPC, as measured by the fearful > neutral face image contrasts, predicted lower PTSD symptom severity at two-weeks -concurrent with the timing of the fMRI scan. The effects are shown in A) left anterior HPC, B) left posterior HPC. HPC: Hippocampus; PTSD: Post-traumatic stress disorder.

Figure 3. Fear-potentiated startle interacts with transient hippocampal threat reactivity in predicting PTSD at two-weeks. Increased FPS differentiation between danger (CS+) and safety (CS-) cues had a significant effect on the inverse relationship between the increased hippocampal threat reactivity and lower PTSD symptoms at two weeks in A) left anterior HPC, B) left posterior HPC. FPS: Fear-potentiated startle; HPC: hippocampus; PTSD: Post-traumatic stress disorder.

883 Figure 4. Effects of sustained hippocampal activity. Increased sustained threat-related activity in
884 A) left posterior HPC and B) right posterior HPC predicted higher PTSD symptoms at two-
885 weeks. Increased FPS differentiation between danger (CS+) and safety (CS-) cues had a
886 significant effect on the relationship between the increased hippocampal threat reactivity and
887 increased PTSD symptoms at two weeks in C) left posterior HPC, right posterior HPC. FPS:
888 Fear-potentiated startle; HPC: hippocampus; PTSD: Post-traumatic stress disorder.
889

890 Table 1. Demographic and Clinical Characteristics

Characteristics	Mean (SD) or *n* (%)
Age, Years	35.19 (12.51)
Gender, Female/Male	76 (65%), 41 (35%)
Race	
Black	53 (45%)
White	41 (35%)
Hispanic/Latino	18 (15%)
Other	4 (5%)
Family Income	
$19,000 or less	32 (27%)
Between $19,001 and $35,000	32 (27%)
Between $35,001 and $50,000	19 (16%)
Between $50,001 and $75,000	10 (9%)
Between $75,001 and $100,000	7 (6%)
Greater than $100,000	14 (12%)
Highest Education Completed	
Some High School	6 (5%)
High School	23 (20%)
Associate Degree	11 (9%)
Bachelor's Degree	19 (16%)
Master's Degree	8 (7%)
Professional School Degree	2 (2%)

Doctoral Degree	1 (1%)
Clinical Characteristics	
PTSD Symptom Severity	
PCL-5 Total Scores at 2 Weeks (n=116)	27.95 (16.53)
PCL-5 Total Scores at 3 Months (n=116)	23.03 (16.59)
Trauma Type	
Motor Vehicle Collision	87 (74%)
Physical Assault	15 (12%)
Sexual Assault	2 (2%)
Fall	6 (5%)
Non-Motorized Collision	2 (2%)
Burns	1 (1%)
Other	4 (3 %)

PCL-5, PTSD Symptom Checklist for DSM-5

894 Table 2. MRI Scan Sequence Parameters by Site

	SITE1 SIEMENS TIM 3T TRIO (12 CHANNEL HEAD COIL)	SITE2 SIEMENS TIM 3T TRIO (12 CHANNEL HEAD COIL)	SITE3 SIEMENS MAGNETOM 3T PRISMA (20 CHANNEL HEAD COIL)	SITE4 SIEMENS 3T VERIO (12 CHANNEL HEAD COIL)
MODALITY				
T1-WEIGHTED	TR = 2530ms, TEs = 1.74/3.6/5.46/7.32 ms, TI = 1260ms, flip angle = 7, FOV = 256mm, slices = 176, Voxel size = 1mm x 1mm x 1mm	TR = 2530ms, TEs = 1.74/3.6/5.46/7.32 ms, TI = 1260ms, flip angle = 7, FOV = 256mm, slices = 176, Voxel size = 1mm x 1mm x 1mm	TR = 2300ms, TE = 2.96ms, TI = 900ms, flip angle = 9, FOV = 256mm, slices = 176, Voxel size = 1.2mm x 1.0mm x 12mm	TR = 2530ms, TEs = 1.74/3.65/5.51/7.72ms, TI = 1260ms, flip angle = 7, FOV = 256mm, slices = 176, Voxel size = 1mm x 1mm x 1mm
FUNCTIONAL MRI	TR = 2360ms, TE = 30ms, flip angle = 70, FOV = 212mm,	TR = 2360ms, TE = 30ms, flip angle = 70, FOV = 212mm,	TR = 2360ms, TE = 29ms, flip angle = 70, FOV = 212mm,	TR = 2360ms, TE = 30ms, flip angle = 70, FOV = 212mm,

	slices = 44, Voxel size = 3mm x 2.72mm x 2.72mm, 0.5 mm gap	slices = 44, Voxel size = 3mm x 3mm x 3mm, 0.5 mm gap	slices = 44, Voxel size = 3mm x 2.72mm x 2.72mm, 0.5 mm gap	slices = 42, Voxel size = 3mm x 2.72mm x 2.72mm, 0.5 mm gap

895

896

897 Table 3. Predicting PTSD Symptoms at 2-Weeks from Transient Hippocampal Threat (F>N)

898 Reactivity and Fear-Potentiated Startle (FPS) Differentiation between Danger (CS+) and Safety

899 (CS-)

	PTSD Symptoms at 2-Weeks Estimate (SE)					
Left aHPC (std)	-0.081*** (0.018)				-0.031 (0.021)	
Right aHPC (std)		-0.022 (0.018)				
Left pHPC (std)			-0.085*** (0.018)			-0.058*** (0.021)
Right pHPC (std)				-0.035 (0.018)		
FPS Diff. (std)					0.038 (0.023)	0.034 (0.022)
Age (std)	0.046** (0.018)	0.044* (0.018)	0.040* (0.018)	0.042* (0.018)	0.010 (0.020)	0.027 (0.020)
Female	0.142*** (0.041)	0.188*** (0.039)	0.187*** (0.039)	0.193*** (0.039)	0.287*** (0.048)	0.347*** (0.047)
Scanner: TrioTim (> Prisma)	-0.095* (0.043)	-0.055 (0.042)	-0.063 (0.042)	-0.063 (0.042)	0.075 (0.051)	0.102* (0.050)
Scanner: Verio (> Prisma)	0.015 (0.048)	0.047 (0.048)	0.037 (0.048)	0.036 (0.048)	0.183*** (0.053)	0.174*** (0.052)
Left aHPC (std): FPS Diff. (std)					-0.041* (0.017)	
Left pHPC (std): FPS Diff. (std)						-0.092*** (0.028)
Constant	3.269*** (0.045)	3.217*** (0.044)	3.220*** (0.044)	3.219*** (0.044)	3.010*** (0.054)	2.957*** (0.055)
Observations	116	116	116	116	94	94
Log Likelihood	-836.337	-845.250	-834.567	-844.101	-619.638	-615.919
Pseudo R^2	0.05	0.04	0.05	0.04	0.10	0.11
Akaike Inf. Crit.	1,684.674	1,702.500	1,681.133	1,700.202	1,255.276	1,247.838

Note 1: $^{*}p<0.05$ $^{**}p<0.01$ $^{***}p<0.005$

Note 2: aHPC: anterior hippocampus; pHPC: posterior hippocampus; std: Standardized; F>N: Fearful > Neutral contrast; FPS Diff: Fear-Potentiated Startle Difference

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902 Table 4. Predicting PTSD Symptom Change across Time from Transient Hippocampal Threat
903 Reactivity and Fear-Potentiated Startle (FPS) Differentiation between Danger (CS+) and Safety
904 (CS-)

	PTSD Symptoms at 2-Weeks Estimate (SE)			
Time	-0.134*** (0.034)	-0.134*** (0.034)	-0.174*** (0.042)	-0.167*** (0.041)
Left aHPC (std)	-0.036 (0.078)		0.026 (0.086)	
Left pHPC (std)		-0.015 (0.076)		0.055 (0.084)
FPS Diff. (std)			0.078 (0.092)	0.104 (0.090)
Age (std)	0.063 (0.065)	0.060 (0.065)	0.035 (0.068)	0.050 (0.069)
Female	-0.045 (0.073)	-0.072 (0.069)	-0.108 (0.077)	-0.147* (0.075)
Scanner: TrioTim (> Prisma)	0.021 (0.098)	-0.003 (0.096)	-0.110 (0.103)	-0.120 (0.101)
Scanner: Verio (> Prisma)	-0.057 (0.090)	-0.042 (0.089)	0.005 (0.094)	0.032 (0.097)
Time: Left aHPC (std)	0.049 (0.033)		0.059 (0.041)	
Time: Left pHPC (std)		0.051 (0.034)		0.078 (0.041)
Time: FPS Diff. (std)			0.015 (0.045)	0.039 (0.043)
Left aHPC (std): FPS Diff. (std)			-0.088 (0.071)	
Time: Left aHPC (std): FPS Diff. (std)			-0.025 (0.035)	
Left pHPC (std): FPS Diff. (std)				-0.077 (0.107)

Time: Left pHPC (std): FPS Diff. (std)				0.025 (0.050)
Constant	2.962*** (0.081)	2.953*** (0.081)	2.854*** (0.087)	2.846*** (0.087)
Observations	321	321	261	261
Log Likelihood	-1,301.706	-1,301.979	-1,045.663	-1,045.059
Akaike Inf. Crit.	2,625.412	2,625.959	2,121.326	2,120.118
Bayesian Inf. Crit.	2,666.898	2,667.445	2,174.794	2,173.586

Note: *p<0.05 **p<0.01 ***p<0.005

Note 2: *aHPC: anterior hippocampus; pHPC: posterior hippocampus; std: Standardized; F>N: Fearful > Neutral contrast; FPS Diff: Fear-Potentiated Startle Difference*

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906

907 Table 5. Predicting PTSD Symptoms at 2-Weeks from Sustained Hippocampal Threat Reactivity

908 and Fear-Potentiated Startle (FPS) Differentiation between Danger (CS+) and Safety (CS-)

	PTSD Symptoms at 2-Weeks Estimate (SE)			
Left pHPC (std)	0.047** (0.018)		0.040 (0.020)	
Right pHPC (std)		0.055*** (0.017)		0.054** (0.021)
FPS Diff. (std)			0.079*** (0.019)	0.054** (0.020)
Age (std)	0.041* (0.018)	0.041* (0.018)	0.019 (0.020)	0.012 (0.020)
Female	0.198*** (0.039)	0.203*** (0.039)	0.343*** (0.046)	0.331*** (0.046)
Scanner: TrioTim (> Prisma)	-0.046 (0.042)	-0.048 (0.042)	0.089 (0.050)	0.110* (0.051)
Scanner: Verio (> Prisma)	0.034 (0.047)	0.019 (0.047)	0.166*** (0.051)	0.193*** (0.055)
Left pHPC (std): FPS Diff. (std)			0.042* (0.018)	
Right pHPC (std): FPS Diff. (std)				0.036* (0.015)
Constant	3.210*** (0.044)	3.211*** (0.044)	2.975*** (0.054)	2.964*** (0.054)
Observations	116	116	94	94
Pseudo R^2	0.04	0.04	0.10	0.11
Log Likelihood	-840.843	-839.448	-617.834	-614.325
Akaike Inf. Crit.	1,693.687	1,690.896	1,251.667	1,244.650
Note 1:				*p<0.05 **p<0.01 ***p<0.005
Note 2:	aHPC: anterior hippocampus; pHPC: posterior hippocampus; std: Standardized; F>N: Fearful > Neutral contrast; FPS Diff: Fear-Potentiated Startle Difference			

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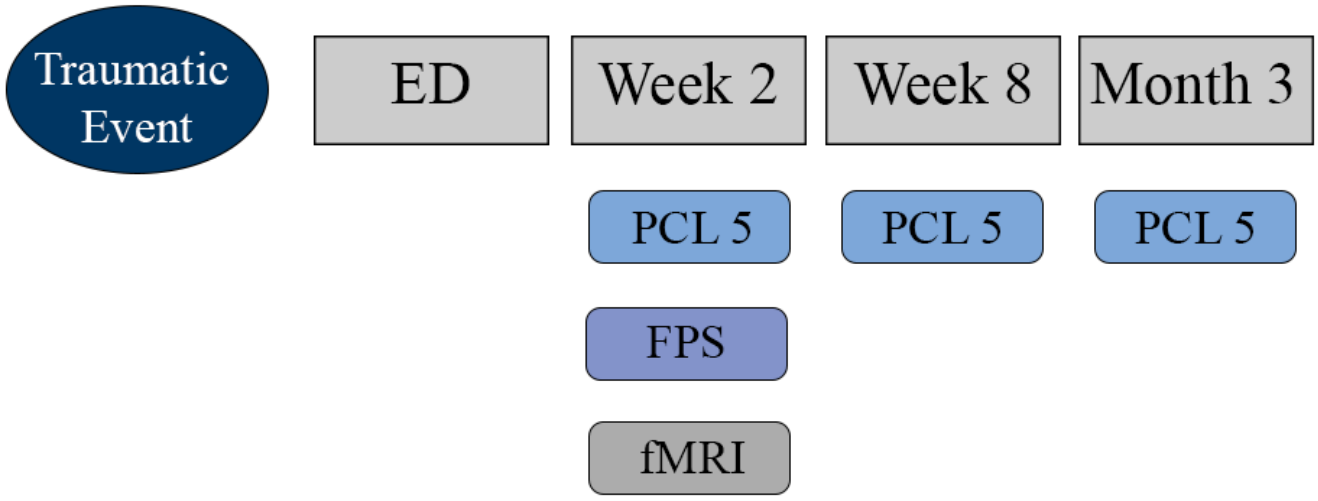

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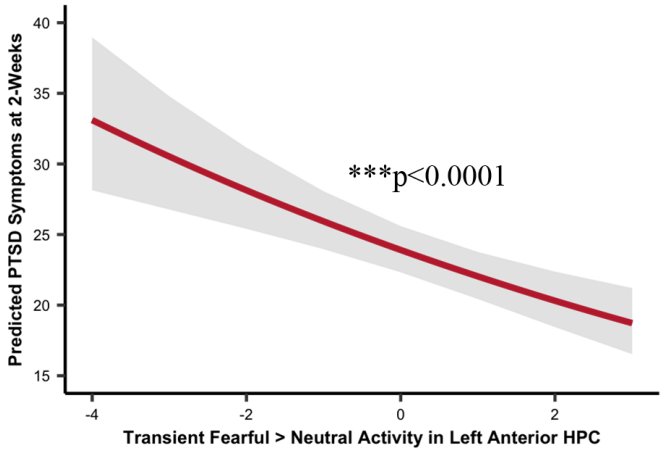

B.