Hippocampal Threat Reactivity Interacts with Physiological Arousal to Predict PTSD Symptoms

Büşra O. Tanriverdi[1], David F. Gregory[1], Timothy D. Ely BA[2], Nathaniel G. Harnett PhD[3,4], Sanne J. H. van Rooij PhD[2], Lauren A.M. Lebois PhD[3,4], Antonia V. Seligowski PhD[3,4], Tanja Jovanovic PhD[5], Kerry J. Ressler MD, PhD[3,4], Stacey L. House MD, PhD[6], Francesca L. Beaudoin MD, PhD[7], Xinming An PhD[8], Thomas C. Neylan MD[9], Gari D. Clifford DPhil[10,11], Sarah D. Linnstaedt PhD[8], Laura T. Germine PhD[12,4], Kenneth A. Bollen PhD[13], Scott L. Rauch MD[14,4], John P. Haran MD, PhD[15], Alan B. Storrow MD[16], Christopher Lewandowski MD[17], Paul I. Musey Jr. MD[18], Phyllis L. Hendry MD[19], Sophia Sheikh MD[19], Christopher W. Jones MD[20], Brittany E. Punches PhD, RN[21,22], Michael C. Kurz MD[23,24,25], Meghan E. McGrath MD[26], Lauren A. Hudak MD, MPH[27], Jose L. Pascual MD, PhD[28,29], Mark J. Seamon MD[30,29], Elizabeth M. Datner MD[31,32], Claire Pearson MD[33], Robert M. Domeier MD[34], Niels K. Rathlev MD[35], Brian J. O'Neil MD[33], Leon D. Sanchez MD, MPH[36,37], Steven E. Bruce PhD[38], Mark W. Miller PhD[39,40], Robert H. Pietrzak PhD, MPH[41,42], Jutta Joormann PhD[43], Deanna M. Barch PhD[44], Diego A. Pizzagalli PhD[3,4], John F. Sheridan PhD[45,46], Jordan W. Smoller MD[47,48], Steven E. Harte PhD[49,50], James M. Elliott PhD[51,52,53], Samuel A. McLean MD, MPH[54,8], Ronald C. Kessler PhD[55], Karestan C. Koenen PhD[56], Jennifer S. Stevens PhD[2], Vishnu P. Murty PhD*[1]

[1]Department of Psychology, Temple University, Philadelphia, PA, 19121, USA, [2]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, 30329, USA, [3]Division of Depression and Anxiety, McLean Hospital, Belmont, MA, 02478, USA, [4]Department of Psychiatry, Harvard Medical School, Boston, MA, 02115, USA, [5]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MA, 48202, USA, [6]Department of Emergency Medicine, Washington University School of Medicine, St. Louis, MO, 63110, USA, [7]Department of Emergency Medicine & Department of Health Services, Policy, and Practice, The Alpert Medical School of Brown University, Rhode Island Hospital and The Miriam Hospital, Providence, RI, 02930, USA, [8]Institute for Trauma Recovery, Department of Anesthesiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27559, USA, [9]Departments of Psychiatry and Neurology, University of California San Francisco, San Francisco, CA, 94143, USA, [10]Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, 30332, USA, [11]Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, 30332, USA, [12]Institute for Technology in Psychiatry, McLean Hospital, Belmont, MA, 02478, USA, [13]Department of Psychology and Neuroscience & Department of Sociology, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27559, USA, [14]Institute for Technology in Psychiatry/Department of Psychiatry, McLean Hospital, Belmont, MA, 02478, USA, [15]Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, MA, 01655, USA, [16]Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN, 37232, USA, [17]Department of Emergency Medicine, Henry Ford Health System, Detroit, MI, 48202, USA, [18]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, 46202, USA, [19]Department of Emergency Medicine, University of Florida College of Medicine -Jacksonville, Jacksonville, FL, 32209, USA, [20]Department of Emergency Medicine, Cooper Medical School of Rowan University, Camden, NJ, 08103, USA, [21]Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, 45267, USA, [22]College of Nursing, University of

Cincinnati, Cincinnati, OH, 45221, USA, [23]Department of Emergency Medicine, University of Alabama School of Medicine, Birmingham, AL, 35294, USA, [24]Department of Surgery, Division of Acute Care Surgery, University of Alabama School of Medicine, Birmingham, AL, 35294, USA, [25]Center for Injury Science, University of Alabama at Birmingham, Birmingham, AL, 35294, USA, [26]Department of Emergency Medicine, Boston Medical Center, Boston, MA, 02118, USA, [27]Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA, 30329, USA, [28]Department of Surgery, Department of Neurosurgery, University of Pennsylvania, Pennsylvania, PA, 19104, USA, [29]Perelman School of Medicine, University of Pennsylvania, Pennsylvania, PA, 19104, USA, [30]Department of Surgery, Division of Traumatology, Surgical Critical Care and Emergency Surgery, University of Pennsylvania, Pennsylvania, PA, 19104, USA, [31]Department of Emergency Medicine, Einstein Healthcare Network, Pennsylvania, PA, 19141, USA, [32]Department of Emergency Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Pennsylvania, PA, 19107, USA, [33]Department of Emergency Medicine, Wayne State University, Detroit, MA, 48202, USA, [34]Department of Emergency Medicine, Saint Joseph Mercy Hospital, Ypsilanti, MI, 48197, USA, [35]Department of Emergency Medicine, University of Massachusetts Medical School-Baystate, Springfield, MA, 01107, USA, [36]Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA, [37]Department of Emergency Medicine, Harvard Medical School, Boston, MA, 02115, USA, [38]Department of Psychological Sciences, University of Missouri - St. Louis, St. Louis, MO, 63121, USA, [39]National Center for PTSD, Behavioral Science Division, VA Boston Healthcare System, Boston, MA, 02130, USA, [40]Department of Psychiatry, Boston University School of Medicine, Boston, MA, 02118, USA, [41]National Center for PTSD, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven, CT, 06516, USA, [42]Department of Psychiatry, Yale School of Medicine, West Haven, CT, 06510, USA, [43]Department of Psychology, Yale University, West Haven, CT, 06520, USA, [44]Department of Psychological & Brain Sciences, Washington University in St. Louis, St. Louis, MO, 63130, USA, [45]Department of Biosciences, OSU Wexner Medical Center, Columbus, OH, 43210, USA, [46]Institute for Behavioral Medicine Research, OSU Wexner Medical Center, Columbus, OH, 43211, USA, [47]Department of Psychiatry, Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, 02114, USA, [48]Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, 02142, USA, [49]Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, MI, 48109, USA, [50]Department of Internal Medicine-Rheumatology, University of Michigan Medical School, Ann Arbor, MI, 48109, USA, [51]Kolling Institute of Medical Research, University of Sydney, St Leonards, New South Wales, 2065, Australia, [52]Faculty of Medicine and Health, University of Sydney, Camperdown, New South Wales, 2006,, Australia, [53]Physical Therapy & Human Movement Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL, 60208, USA, [54]Department of Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27559, USA, [55]Department of Health Care Policy, Harvard Medical School, Boston, MA, 02115, USA, [56]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, 02115, USA

*Denotes Corresponding Author

Corresponding author:

Vishnu P. Murty
Rm 532, Weiss Hall
1701 N. 13th Street
Philadelphia, PA
19122
(t): 215-204-4940
(e): Vishnu.murty@temple.edu

Number of pages: 42
Number of figures: 4
Number of tables: 2
Number of words in abstract: 142
Number of words in introduction: 649
Number of words in discussion: 1500

Conflict of Interest: Dr. Ressler has served on advisory boards for Takeda, Resilience Therapeutics, Janssen and Verily/Google. His research has been sponsored by Alkermes and Brainsway and he has worked as a consultant for Alkermes. In the last three years, Dr. Clifford has received research funding from the NSF, NIH and LifeBell AI, and unrestricted donations from AliveCor, Amazon Research, the Center for Discovery, the Gordon and Betty Moore Foundation, MathWorks, Microsoft Research, the Gates Foundation, Google, One Mind Foundation, and Samsung Research. Dr. Clifford has financial interest in AliveCor and receives unrestricted funding from the company. He also is the CTO of MindChild Medical and CSO of LifeBell AI and has ownership in both companies. These relationships are unconnected to the current work. Dr. Germine is on the scientific advisory board of the nonprofit Sage Bionetworks, for which she receives a small honorarium. Dr. Sheikh has received funding from the Florida Medical Malpractice Joint Underwriter's Association Dr. Alvin E. Smith Safety of Healthcare Services Grant, Allergan Foundation, the NIH/NIA-funded Jacksonville Aging Studies Center (JAX-ASCENT; R33AG05654), the Substance Abuse and Mental Health Services Administration (1H79TI083101-01), and the Florida Blue Foundation. Dr. Jones reports no direct conflicts related to this paper, and no ongoing conflicts. He has been an investigator on studies funded by Hologic Inc, Janssen, and AstraZeneca, for which his department has received research funding. Over the past 3 years, Dr. Pizzagalli has received consulting fees from BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Concert Pharmaceuticals, Engrail Therapeutics, Neurocrine Biosciences, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes, and research funding from 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. Dr. Elliott reports support from the National Institutes of Health (NIH) through Grant Numbers R01HD079076 & R03HD094577, Eunice Kennedy Shriver National Institute of Child Health & Human Development, National Center for Medical Rehabilitation Research, and South Wales Health Spinal Cord Injury Research Grants Program.

In the past 3 years, Dr. Kessler was a consultant for Datastat, Inc., RallyPoint Networks, Inc., Sage Pharmaceuticals, and Takeda. The remaining authors report no financial relationships with commercial interests.

Acknowledgments: This study is supported by the National Institute of Mental Health U01MH110925 (to Kerry J. Ressler), K00MH119603 (to Nathaniel G. Harnett), K01MH118467 (to Lauren A. M. Lebois), the US Army Medical Research and Material Command, The One Mind Foundation, and The Mayday Fund. Verily Life Sciences and Mindstrong Health provided some of the hardware and software used to perform study assessments. Data and/or research tools used in the preparation of this manuscript were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA). NDA is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Dataset identifier(s): *DOI 10.15154/1521128.* This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDA. Support for title page creation and format was provided by AuthorArranger, a tool developed at the National Cancer Institute. The investigators wish to thank the trauma survivors participating in the AURORA Study. Their time and effort during a challenging period of their lives make our efforts to improve recovery for future trauma survivors possible.

Abstract

Prior studies highlight how threat-related arousal may impair hippocampal function. Hippocampal impairments are reliably associated with post-traumatic stress disorder (PTSD); however, little research has characterized how increased threat-sensitivity may drive arousal responses to alter hippocampal reactivity, and further how these alterations relate to the sequelae of trauma-related symptoms. In a sample of individuals recently exposed to trauma (N=117, 76 Female), we found that PTSD symptoms at 2-weeks and 3-months were associated with decreased hippocampal responses to threat as assessed with functional magnetic resonance imaging (fMRI). Further, decreased hippocampal threat sensitivity was predicted by individual differences in fear-potentiated startle, an arousal-mediated behavior. Critically, the relationship between hippocampal threat sensitivity and PTSD symptomology only emerged in individuals who showed high threat-related arousal. 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 are 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 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). Although moderate amounts of threat increase hippocampal sensitivity (Joëls et al., 2006), excessive threat has a detrimental effect on hippocampal function (Kim & Diamond, 2002; McEven, 2007; Henckens et al., 2009; Schwabe & Wolf, 2012; Bisby & Burgess, 2013, 2017). In PTSD, decreased hippocampal engagement is thought to enable traumatic memories to persist (Hayes et al., 2011) and impair the ability to discriminate between danger and safety, leading to the overgeneralization of fear (Besnard & Sahay, 2016; Asok et al., 2019), which underlies PTSD symptoms (e.g., Hayes et al., 2011). Prior studies have also associated lower hippocampal engagement during inhibitory tasks with chronic PTSD (van Rooij et al., 2016) and PTSD development (van Rooij, 2018). However, others reported increased hippocampus activation in individuals with PTSD when remembering emotionally valenced word pairs that resemble the traumatic experience (Bremner et al., 2003) or when seeing trauma-related imagery (earthquake in this case) (Tural et al, 2018). These inconsistencies may be due to the functional demands placed on the hippocampus, in particular those studying memory retrieval. Here, we characterize the relationship amongst hippocampal function, threat sensitivity, and PTSD symptomology in a large sample of recently traumatized civilians.

Out laboratory has previously developed a model of how threat-related arousal disrupts hippocampal function, biasing information processing away from hippocampus to other learning structures, predominantly due to arousal-mediated engagement of the norepinephrine (NE) system (Murty & Adcock, 2017; Clewett & Murty, 2019). Our model predicts that threat increases physiological arousal, disrupting behavioral and neural indices of intact hippocampal

function. Accordingly, hippocampus activity is impaired (Kim & Diamond, 2002), and hence, hippocampus-reliant memory integration is disrupted (Clewett & Murty, 2019). This model posits that an individual's threat sensitivity, including heightened arousal responses, can determine downstream impairments in hippocampal function (Murty & Adcock, 2017).

Threat-predictive behaviors such as fear-potentiated startle responses to reinforced and non-reinforced stimuli (henceforth 'danger' and 'safety', respectively) are heightened in PTSD (Grillon & Morgan, 1999; Grillon & Baas, 2003; Glover et al., 2011; Norrholm & Jovanovic, 2018), and may be linked with corresponding increases in NE activation (Yehuda et al., 1996). Previous research found 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 when a threat cue no longer indicates danger (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). In light of our model, these increases in arousal may divert information processing resources away from the hippocampus during threat, making individuals more susceptible to PTSD development.

In the current design, we extend our model to trauma-related behavioral impairment, by characterizing hippocampal dysfunction in relation to heightened arousal and PTSD symptom severity in a group of recently trauma-exposed participants. We operationalize hippocampal threat sensitivity as hippocampal responses to fearful versus neutral face stimuli with functional imaging, and arousal as fear-potentiated startle responses to learned danger cues. We also make a distinction between the anterior and posterior portions of the hippocampus, following their differential engagement in fear learning (Bannerman et al., 2004; Dolcos et al., 2004; Murty et

al., 2010; Strange et al., 2014), and attempt to replicate earlier findings relating changes in the hippocampal subregions to changes in PTSD symptomology (Hayes et. al., 2011; Abdallah et al., 2017). We hypothesized that 1) reductions in hippocampus (HPC) threat sensitivity will predict PTSD symptom severity in trauma-exposed individuals; 2) associations with PTSD symptoms will be greater in the anterior (aHPC) versus posterior (pHPC) hippocampus, and 3) associations between HPC-threat sensitivity and PTSD symptoms will be mediated by fear-potentiated startle responses.

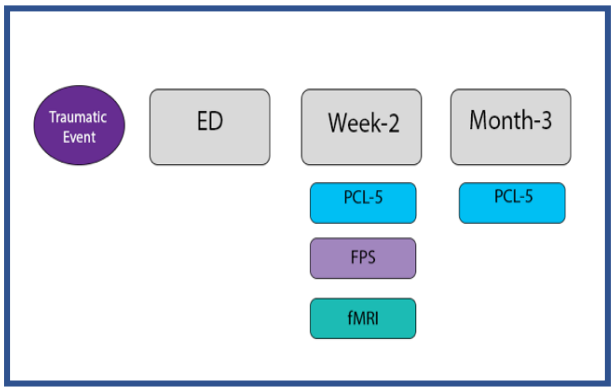


Figure 1. Experimental Timeline. Participants were recruited from emergency departments after exposure to trauma. Trauma symptoms were assessed two-weeks and three-months post-trauma using PCL-5. As part of the two-weeks assessments, participants also completed a fear conditioning task, and a face viewing 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.

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 *M(SD)*=18(6) days later 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 seventeen 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 analyses focused on the symptom severity at 2-weeks and 3-months after trauma exposure (Figure 1).

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=117)	27.95 (16.53)
PCL-5 Total Scores at 3 Months (n=117)	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

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 difference score by subtracting average startle magnitude to the NA trials from average startle magnitude to the CS+ (danger signal) and CS- (safety signal).

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 10th 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 (T1-w) 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 pre-processing stream. FMRI preprocessing was calculated 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 4D slice timing, head motion correction, non-linear warping to the MNI space, and nuisance regression based on head motion (6 degrees of

translation/motion and their first derivative) and non-gray matter signal (white matter and csf, and their first derivative). Following pre-processing, we modelled event-evoked responses to fearful and neutral blocks of faces using FEAT version 6.0 as implemented in FSL 6.0.1. Time series statistical analyses used GLMs to model a total of 24 regressors, including blocks of fearful images, blocks of neutral images. The duration of events was modelled as separate regressors and were convolved with a double-gamma hemodynamic response function. 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.

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, slices = 44, Voxel size = 3mm x 2.72mm x 2.72mm, 0.5 mm gap	TR = 2360ms, TE = 30ms, flip angle = 70, FOV = 212mm, slices = 44, Voxel size = 3mm x 3mm x 3mm, 0.5 mm gap	TR = 2360ms, TE = 29ms, flip angle = 70, FOV = 212mm, slices = 44, Voxel size = 3mm x 2.72mm x 2.72mm, 0.5 mm gap	TR = 2360ms, TE = 30ms, flip angle = 70, FOV = 212mm, slices = 42, Voxel size = 3mm x 2.72mm x 2.72mm, 0.5 mm gap

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 anterior and posterior hippocampus in two separate models. Laterality was added into the models as an interaction term to test whether the effects were specific to the right or left hemisphere. Then, we assessed if fear-related activity (fearful>neutral) in the anterior and posterior portions of the hippocampus predicted the participants' PTSD symptom severity at 2 weeks and 3 months. To do so, we first tested a base model where the independent variable was the fear related activity in the anterior and posterior hippocampus collapsed together. Using a mixed-effects linear model we tested a second model with a control variable of ROI (anterior, posterior). By comparing the two models we evaluated whether adding the particular ROIs improved the fit of our base model using an omnibus chi-squared test. Model fit comparisons were described using the Bayesian information criterion (BIC; Schwarz, 1978). Significance was set at $p < 0.05$ (uncorrected), and trends at $p < 0.10$. Bonferroni corrections for multiple comparisons (4 models) were set at $p < 0.0125$. Age and gender were added in all of the models as covariates.

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 also predicted the PTSD

symptoms at two-weeks and three-months post-trauma. Here we tested a total of four models, with significance set at $p < 0.005$ (uncorrected) and Bonferroni correction set at $p < 0.0125$.

The unstandardized beta coefficients are reported for all our significant results. All analyses were performed using R software (R package version 3.4.1) using the anova (the stats library), lm (the stats library), and lmer (the lme4 library) functions depending on the test. Analysis scripts are available upon request.

Results

Greater hippocampus responses to fearful than neutral faces

A repeated measures two-way ANOVA on emotion (fearful, neutral) by laterality (right, left) revealed a main effect of emotion (anterior: $\beta = 0.021$, $F(1,464) = 5.08$, $SE = 0.009$, $p = 0.025$; posterior: $\beta = 0.08$, $F(1,464) = 57.72$, $SE = 0.01$, $p = 0.000$). Post hoc analyses with paired t-tests (Tukey adjusted) showed that there were greater responses to fearful than neutral faces (anterior: $t(348) = 2.25$, $p = 0.025$; posterior: $t(348) = 7.6$, $p = 0.0001$). The main effects of laterality or emotion by laterality interaction were not significant in either of the hippocampus sub-regions, therefore we collapsed across the anterior and posterior hippocampus for all future analyses.

Decreased hippocampal fear-related activity predicts PTSD symptoms

Threat-related activity in the left hippocampus, collapsed across anterior and posterior portions, was associated with PTSD symptom severity at 2-weeks ($\beta = -22.77$, $F(2,234) = -2.76$, $SE = 8.24$, $p = 0.006$; Figure 2a), such that reduced fear reactivity predicted greater PTSD symptoms. Model fits did not increase when hippocampal region (anterior, posterior) was added as the interaction term into the second model (BIC w/o ROIs: 1993; BIC w/ ROIs: 2003; model

comparison $\chi^2(2) = 0.03$, $p = 0.98$), suggesting an equivalent role for anterior and posterior hippocampus. Similarly, activity across anterior and posterior portions of the left hippocampus was significantly associated with PTSD symptoms at 3-months ($\beta = -23.61$, $F(2,234) = -2.85$, $SE = 8.3$, $p = 0.005$, Figure 2b) and adding the ROIs into the model did not increase the model fit (BIC w/o ROIs: 1995; BIC w/ ROIs: 2006; model comparison $\chi^2(2) = 0.16$, $p = 0.92$). Relationships between right hippocampal fear reactivity and PTSD were non-significant. Both models that showed a significant effect of threat-related activity in left hippocampus in predicting PTSD symptoms at 2-weeks and 3-months survived the Bonferroni correction ($p = 0.0125$).

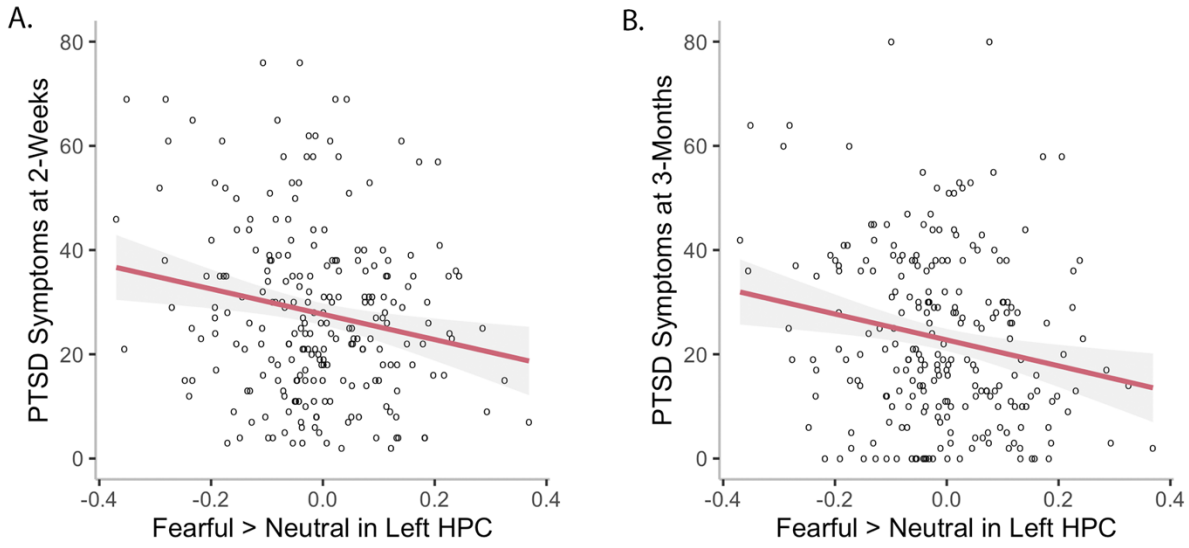


Figure 2. Reduced threat related activity in left hippocampus predicts PTSD severity. Threat-related activity in left hippocampus, as measured by the fearful > neutral face image contrasts, predicted PTSD symptom severity **A)** at two-weeks -concurrent with the timing of the fMRI scan ($p = 0.006$) and **B)** at three-months post-trauma ($p = 0.005$). HPC: Hippocampus; PTSD: Post-traumatic stress disorder.

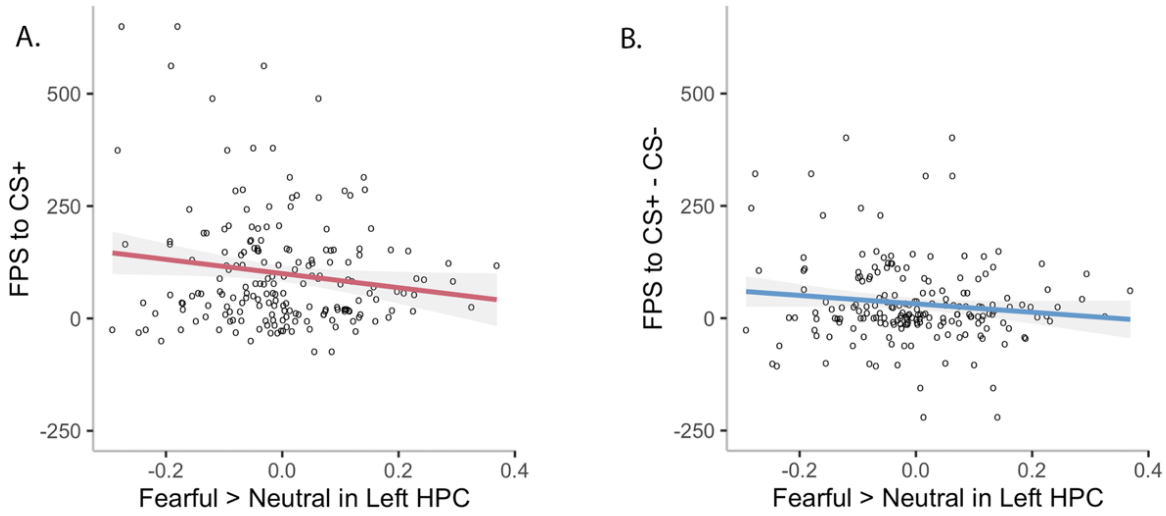


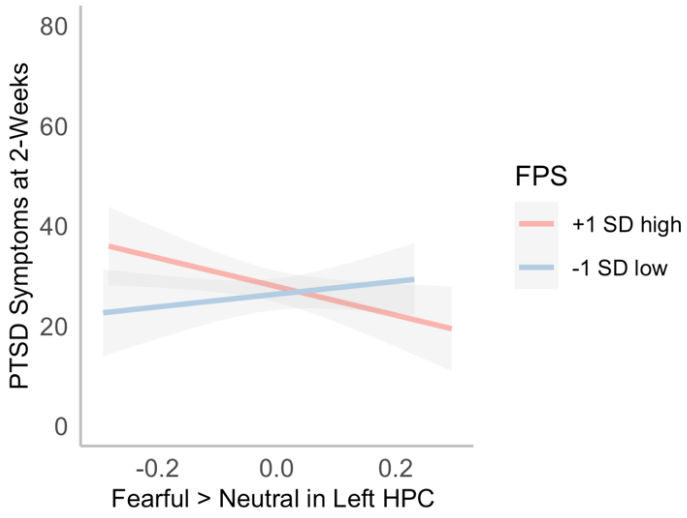
Figure 3. Threat-related activity in left hippocampus predicts fear-potentiated startle responses. **A)** Fear-potentiated startle responses to the CS+ ($p = 0.001$). **B)** The difference between the fear-potentiated startle responses to the CS+ and CS- ($p = 0.07$). FPS: Fear-potentiated startle; CS+: conditioned stimulus paired with aversive air blast; CS-: conditioned stimulus not paired with aversive air blast.

Fear-related activity in the hippocampus predicted startle responses during fear acquisition

Participants had greater fear-potentiated startle (FPS) response to the CS+ compared to the CS- ($t(94) = 3.42$, $p = 0.001$) during fear acquisition, suggesting that they learned to discriminate between the danger and safety cues. Interestingly, higher threat-related activity in the left hippocampus, collapsed across anterior and posterior portions, was significantly associated with lower fear-potentiated startle responses to the CS+ ($\beta = -179.24$, $F(2,190) = -2.34$, $SE = 76.72$, $p = 0.021$; Figure 3a), and showed a trend towards predicting a difference between danger and safety signals ($\beta = -100.53$, $F(2,190) = -1.83$, $SE = 55.07$, $p = 0.07$, Figure 3b). These findings suggest individuals showing greater threat anticipation during fear-conditioning had lower threat reactivity in the hippocampus. Critically, we found an interaction between threat-related hippocampal activity and FPS in predicting 2-week PTSD symptoms ($\beta = -0.25$, $F(2,190) = -2.67$, $SE = 0.09$, $p = 0.008$); such that individuals with greater FPS differentiation between CS+ and CS- (i.e., Danger - Safety cues) had a stronger relationship

between decreased reactivity to threat cues in the hippocampus and PTSD symptoms (Figure 4). Neither the FPS to the danger cues nor the FPS differentiation between danger and safety cues were related to the PTSD symptoms at 3-months ($p = 0.3$, $p = 0.9$, respectively).

Figure 4. Fear-potentiated startle interacts with hippocampal threat sensitivity in predicting PTSD at two-weeks. FPS: Fear-potentiated startle; HPC: hippocampus.



Discussion

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

We first showed greater hippocampal BOLD responses for fearful compared to neutral faces at the group level, suggesting that the hippocampus was more sensitive to the negative than neutral information (i.e., facial expressions). These findings are in line with earlier trauma studies suggesting that there is an overall increased fear sensitivity towards threatening information after exposure to traumatic events, as evidenced by fear generalization and a failure

to inhibit physiological fear responses to safe stimuli shown by individuals with PTSD (Jovanovic et al., 2010; Jovanovic et al., 2012; Maeng & Milad, 2017). However, given the absence of pre-trauma assessments in the AURORA project, we acknowledge that our study is limited in differentiating whether this hippocampal threat sensitivity is reflective of early effects of the trauma exposure or is a risk factor for PTSD that exist pre-trauma (Pitman et al., 2006).

Importantly, we found that decreased hippocampal threat sensitivity was related to PTSD symptom severity at both two-weeks and three-months after trauma exposure. Specifically, we found that participants who showed reduced threat reactivity in the left hippocampus had more severe PTSD symptoms. This is consistent with previous research that showed reduced left hippocampus activity in PTSD patients when remembering trauma-related memories (Bremner 2001; Bremner et al., 2003; Hayes et al., 2011) or recently learned negative information (Bisby et al., 2017). Reduced hippocampal activation during a response inhibition task has also been associated with increased PTSD symptoms in chronically traumatized individuals (van Rooij et al., 2016; van Rooij & Jovanovic, 2019), and predicted future PTSD symptoms in recently traumatized civilians (van Rooij et al., 2018). Interestingly, these findings are at odds with prior work showing that increased hippocampal activity was positively related to re-experiencing symptoms (Stevens et al., 2018), suggesting that our presented results may not generalize to hippocampal function directly during emotional memory processing. Together with these earlier findings, our study supports an account of intact hippocampal function playing a role in trauma resilience (van Rooij et al., 2021).

An important distinction between our findings and the previous research, however, is that previous research has shown that the association between the hippocampal dysfunction and PTSD was driven by the anterior portion of the hippocampus (Hayes et al., 2011; Dickie et al.,

2011; Abdallah et al., 2017), a region that is often implicated in fear learning (Kjerstrup et al., 2002; Bannerman et al., 2004; Murty et al., 2010; Strange et al., 2014). However, we did not find a functional distinction between anterior and posterior portions of the hippocampus in predicting PTSD symptom severity, however, notably our current sample is larger than prior studies. Therefore, our results are more in line with the results of Lazarov and colleagues (2017), who recently showed that the functional distinction between anterior and posterior hippocampus in their connectivity to regions in the default mode network, e.g., ventromedial prefrontal cortex, precuneus and posterior cingulate cortex, which are often implicated in PTSD patients, is eliminated in individuals with PTSD but not in trauma exposed controls.

Our findings suggest a complex role of the hippocampus in threat sensitivity since it is highly sensitive to threatening stimuli after traumatic experiences. This heightened hippocampal sensitivity protects the individual from developing severe symptoms of PTSD, but only to the extent that it can process the negative information. We found that the relationship between hippocampal threat reactivity and PTSD symptom severity is modulated by increased fear-potentiated startle responses for threat (CS+), and impaired ability to differentiate threat from safety (CS-). Specifically, our data demonstrated greater threat anticipation, as evidenced by the greater fear-potentiated startle responses to CS+, was associated with lower reactivity in the left hippocampus. Moreover, this interaction between the reduced hippocampal reactivity and greater threat anticipation was linked with PTSD symptom severity at two-weeks post-trauma. Although previous research has established an association between reduced hippocampal activity and arousal symptoms of PTSD (Hayes et al., 2011), and between the increased physiological responses to danger 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 the NE system, which in turn prioritizes the most emotionally salient information for encoding event memories (Clewett & Murty, 2019). Critically, PTSD studies have shown increased norepinephrine release in response to stress (see Bremner, 2006 for a review). 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.

Importantly, we did not find the same modulatory effect of arousal on PTSD symptom severity at three-months. One potential explanation could be the perceived proximity of threat (Mobbs et al., 2015): At two weeks after the traumatic event, hyperarousal state may still make people more sensitive to threat, whereas in three months the event is no longer as threatening. However, literature suggests that the detrimental effects of trauma remain longer than only two-weeks, and in some cases the onset of PTSD is delayed more than 6 months, as acknowledged by the DSM-5 as delayed expression (American Psychiatric Association, 2013). Hence, we believe our finding that the physiological arousal at two weeks predicts the PTSD symptom severity at two-weeks but not at three-months does not imply a role for the proximity of threat at the immediate aftermath of the trauma. Rather, we suggest physiological arousal is a state marker of

the concurrent PTSD symptom severity. In our study, fear-potentiated startle responses and the two-week PTSD symptoms were collected at the same time, that is, within the two-weeks of experiencing a traumatic event. We expect fear-potentiated startle responses at three-months, if measured, would predict the symptom severity at three-months. On the other hand, the hippocampal threat sensitivity is a more general marker for PTSD development given our findings that it predicts PTSD symptoms both concurrently (two-weeks) and three-months post-trauma.

Our model further proposed that impaired hippocampal function due to heightened arousal disrupts the hippocampus-reliant memory integration (Clewett & Murty, 2019). Our data were limited in their ability to test this portion of the model, as they did not include a memory retrieval test of the stimuli presented in the scanner, hence limiting our ability to make inferences about how hippocampal impairments relate to deficits in memory integration, i.e., memory fragmentation, or disorganization in PTSD (Brewin et al., 2010). Nevertheless, our finding that impaired hippocampal engagement during threat processing is predictive of PTSD symptom severity has potential implications for the trauma-related memory fragmentation given the hippocampus' role in memory integration (Schlichting & Preston, 2015). Specifically, we suggest hippocampal impairment during encoding disrupts successful integration of traumatic memories into one's life narrative. However, given the shift from the hippocampus to the NE systems, the traumatic events are encoded as highly salient emotional memories. As a result, individuals maintain fragmented but highly salient memories of the traumatic events (Brewin et al., 1996), which they involuntarily and repeatedly re-experience as intrusions or flashbacks (Brewin, 2015). This assumption is in line with the recent memory fragmentation account of PTSD by Brewin (2016), who suggested that individuals are able to recall the global outline of a

traumatic event in a coherent manner in itself, e.g., with the temporal and contextual event details, but when they relive the event, voluntarily or involuntarily, their narratives are fragmented and disorganized. However, to test these types of models, future studies would need to focus more on the structure of narrative recall, rather than re-experiencing more broadly.

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.

References

Abdallah CG, Wrocklage KM, Averill CL, Akiki T, Schweinsburg B, Roy A, Martini B, Soutwick SM, Krystal JH, Scott JC (2017) Anterior hippocampal dysconnectivity in posttraumatic stress disorder: a dimensional and multimodal approach. Transl Psychiatry 7:1-7.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Author

Asok A, Kandel ER, Rayman JB (2019) The Neurobiology of Fear Generalization. Front Behav Neurosci 12:329

Bannerman DM, Rawlins JN, McHugh SB, Deacon RM, Yee BK, Bast T, Zhang WN, Pothuizen HH, Feldon J (2004) Regional dissociations within the hippocampus—memory and anxiety. Neurosci Biobehav Rev 28:273–283.

Besnard A, Sahay A (2016) Adult Hippocampal Neurogenesis, Fear Generalization, and Stress. Neuropsychopharmacology Rev 41:21-44.

Bisby JA, Burgess N (2017) Differential effects of negative emotion on memory for items and associations, and their relationship to intrusive imagery. Curr Opin Behav Sci 17:124-132.

Bisby JA, Burgess N (2013) Negative affect impairs associative memory but not item memory. Learn Mem 2:21-27.

Bremner JD (2001) Hypotheses and controversies related to effects of stress on the hippocampus: An argument for stress-induced damage to the hippocampus in patients with posttraumatic stress disorder. Hippocampus 11:75-81.

Bremner J, Vythilingam M, Vermetten E, Southwick SM, Mcglashan T, Staib LH, Soufer R, Charney DS (2003) Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biological Psychiatry 53:879-889.

Brewin CR (2016) Coherence, disorganization, and fragmentation in traumatic memory reconsidered: A response to Rubin et al (2016). J Abnorm Psychology 125:1011–1017.

Brewin CR (2015) Re-experiencing traumatic events in PTSD: New avenues in research on intrusive memories and flashbacks. Eur J Psychotraumatol 6:27180.

Brewin CR, Gregory JD, Lipton M, Burgess N (2010) Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. Psychol Rev 117:210–232.

Brewin CR, Dalgleish T, Joseph S (1996) A dual representation theory of posttraumatic stress disorder. Psychol Rev 103:670–686.

Briscione MA, Jovanovic T, Norrholm SD (2014) Conditioned fear associated phenotypes as robust, translational indices of trauma-, stressor-, and anxiety-related behaviors. Front Psychiatry 5:88.

Cacciaglia R, Nees F, Grimm O, Ridder S, Pohlack ST, Diener SJ, Liebscher C, Flor H (2017) Trauma exposure relates to heightened stress, altered amygdala morphology and deficient extinction learning: Implications for psychopathology. Psychoneuroendocrinology 76:19–28.

Clewett D, Murty VP (2019) Echoes of Emotions Past: How Neuromodulators Determine What We Recollect. eNeuro 6:1-19.

Delgado MR, Nystrom LE, Fissell C, Noll DC, Fiez JA (2000) Tracking the Hemodynamic Responses to Reward and Punishment in the Striatum. J Neurophysiol 84:3072-3077.

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31:968–980.

Dickie EW, Brunet A, Akerib V, Armony JL (2011) Neural correlates of recovery from post-traumatic stress disorder: A longitudinal fMRI investigation of memory encoding. Neuropsychologia 49:1771-1778.

Dolcos F, LaBar KS, Cabeza R (2004) Interaction between the Amygdala and the Medial Temporal Lobe Memory System Predicts Better Memory for Emotional Events. Neuron 42:855–863.

Eichenbaum H (2001) The hippocampus and declarative memory: Cognitive mechanisms and neural codes. Behav Brain Res 127:199–207.

Ekman P, Friesen WV (1976) Measuring facial movement. J Nonverbal Behav 1:56-75.

Esteban O, Birman D, Schaer M, Koyejo O, O, Poldrack RA, Gorgolewski KJ (2017) MRIQC: Advancing the Automatic Prediction of Image Quality in MRI from Unseen Sites. PLoS One, 12: e0184661.

Glover EM, Phifer JE, Crain DF, Norrholm SD, Davis M, Bradley B, Ressler KJ, Jovanovic T (2011) Tools for translational neuroscience: PTSD is associated with heightened fear responses using acoustic startle but not skin conductance measures. Depress Anxiety 28:1058–1066.

Grillon C, Baas J (2003) A review of the modulation of the startle reflex by affective states and its application in psychiatry. Clin Neurophysiol 114:1557–1579.

Grillon C, Morgan CA (1999) Fear-Potentiated Startle Conditioning to Explicit and Contextual Cues in Gulf War Veterans with Posttraumatic Stress Disorder. J Abnorm Psychol 108:134-42.

Hayes JP, LaBar KS, Mccarthy G, Selgrade E, Nasser J, Dolcos F, Morey RA (2011) Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. J Psychiatric Res 45:660-669.

Henckens MJ, Hermans EJ, Pu Z, Joëls M, Fernández G (2009) Stressed memories: how acute stress affects memory formation in humans. J Neurosci 29:10111–10119.

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 167:748–751.

Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012) FSL. NeuroImage 62:782–790.

Joëls M, Pu Z, Wiegert O, Oitzl MS, Krugers HJ (2006) Learning under stress: how does it work? Trends Cogn Sci 10:152–158.

Jovanovic T, Ely T, Fani N, Glover EM, Gutman D, Tone EB, Norrholm SD, Bradley B, Ressler KJ (2013) Reduced neural activation during an inhibition task is associated with impaired fear inhibition in a traumatized civilian sample. Cortex 49:1884-1891.

Jovanovic T, Kazama A, Bachevalier J, Davis M (2012) Impaired safety signal learning may be a biomarker of PTSD. Neuropharmacology 62:695–704.

Jovanovic T, Norrholm SD, Blanding NQ, Davis M, Duncan E, Bradley B, Ressler KJ (2010) Impaired fear inhibition is a biomarker of PTSD but not depression. Depress Anxiety 27:244–251.

Jovanovic T, Norrholm SD, Blanding NO, Phifer JE, Weiss T, Davis M, Duncan E, Bradley B, Ressler K (2010) Fear potentiation is associated with hypothalamic-pituitary-adrenal axis in PTSD. Psychoneuroendocrinology 35:846-857.

Kerr KM, Agster KL, Furtak SC, Burwell RD (2007) Functional neuroanatomy of the parahippocampal region: the lateral and medial entorhinal areas. Hippocampus 17:697–708

Kim JJ, Diamond DM (2002) The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci 3:453–462.

Kim YJ, van Rooij SJH, Ely TD, Ressler KJ, Jovanovic T, Stevens JS (2019) Association between posttraumatic stress disorder severity and amygdala habituation to fearful stimuli. Depress Anxiety 36:647–658.

Kjelstrup KG, Tuvnes FA, Steffenach HA, Murison R, Moser EI, Moser MB (2002) Reduced fear expression after lesions of the ventral hippocampus. Proc Natl Acad Sci U S A 99:10825–10830.

Lazarov A, Zhu X, Suarez-Jimenez B, Rutherford BR, Neria, Y (2017) Resting-state functional connectivity of anterior and posterior hippocampus in posttraumatic stress disorder. J Psychiatric Res 94:15–22.

Li X, Morgan PS, Ashburner J, Smith J, Rorden C (2016) The first step for neuroimaging data analysis: DICOM to NIfTI conversion. J Neurosci Methods. 264:47-56.

Maren S, Holmes A (2016) Stress and Fear Extinction. Neuropsychopharmacology 41:58–79.

Maeng LY, Milad MR (2017) Post-Traumatic Stress Disorder: The Relationship Between the Fear Response and Chronic Stress. Chronic Stress 1:1-13.

McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87:873–904.

McLean SA et al. (2020) The AURORA Study: A longitudinal, multimodal library of brain biology and function after traumatic stress exposure. Mol Psychiatry 25:283–296.

Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP, Rauch SL (2009) Neurobiological Basis of Failure to Recall Extinction Memory in Posttraumatic Stress Disorder. Biol Psychiatry 66:1075-1082.

Mobbs D, Hagan CC, Dalgleish T, Silston B, Prevost C (2015) The ecology of human fear: Survival optimization and the nervous system. Front Neurosci 9:55.

Murty VP, Shah H, Montez D, Foran W, Calabro F, Luna B (2018) Age-Related Trajectories of Functional Coupling between the VTA and Nucleus Accumbens Depend on Motivational State. J Neurosci 38:7420–7427.

Murty VP**,** Adcock RA (2017) Motivated memory: anticipated reward and punishment shape encoding via differential medial temporal network recruitment. In: The hippocampus from cells to systems (Hannula D, Duff M, eds), pp467-501 New York: Springer, Cham.

Murty VP, Tompary A, Adcock RA, Davachi L (2016) Selectivity in Postencoding Connectivity with High-Level Visual Cortex Is Associated with Reward-Motivated Memory. J Neurosci 37:537–545.

Murty VP, Ritchey M, Adcock RA, LaBar KS (2010) fMRI studies of successful emotional memory encoding: a quantitative meta-analysis. Neuropsychologia 48:3459–3469.

Norrholm SD, Jovanovic T (2018) Fear Processing, Psychophysiology, and PTSD. Harv Rev Psychiatry 26:129–141.

Norrholm SD, Jovanovic T, Olin IW, Sands LA, Karapanou I, Bradley B, Ressler KJ (2011) Fear extinction in traumatized civilians with posttraumatic stress disorder: relation to symptom severity. Biol Psychiatry 69:556–563.

Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, Milad MR, Liberzon I (2012) Biological studies of post-traumatic stress disorder. Nat Rev Neurosci 13:769-787.

Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, Metzger LJ, Shenton ME, Yehuda R, Orr SP (2006) Clarifying the Origin of Biological Abnormalities in PTSD Through the Study of Identical Twins Discordant for Combat Exposure. Annal N Y Acad Sci 1071:242–254.

Poppenk J, Evensmoen HR, Moscovitch M, Nadel L (2013) Long-axis specialization of the human hippocampus. Trends Cogn Sci 17:230-240.

Schwabe L, Wolf OT (2012) Stress modulates the engagement of multiple memory systems in classification learning. J Neurosci 32:11042–11049.

Schawrz, G. (1978). Estimating the dimensions of a model. Annal Statistics 6:461-464.

Shin LM, Liberzon I (2010) The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology 3:169-191.

Schlichting ML, Preston AR (2015) Memory integration: Neural mechanisms and implications for behavior. Curr Opin Behav Sci 1:1–8.

Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, Macklin ML, Lasko NB, Cavanagh SR, Krangel TS, Orr SP, Pitman RK, Whalen, PJ, Rauch SL (2005). A Functional Magnetic Resonance Imaging Study of Amygdala and Medial Prefrontal Cortex Responses to Overtly Presented Fearful Faces in Posttraumatic Stress Disorder. Arch Gen Psychiatry 62:273-281.

Stevens JS, Reddy R, Kim YJ, van Rooij SJ, Ely TD, Hamann S, Ressler KJ, Jovanovic T (2018). Episodic memory after trauma exposure: Medial temporal lobe function is positively related to re-experiencing and inversely related to negative affect symptoms. NeuroImage Clin 17:650-658.

Stevens JS, Jovanovic T, Fani N, Ely TD, Glover EM, Bradley B, Ressler KJ (2013) Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. J Psychiatric Res 47:1469–1478.

Strange BA, Twitter MP, Lein ED, Moser EI (2014) Functional Organization of the Hippocampal Longitudinal Axis. Nat Rev Neurosci 15:655-669.

Tural Ü, Aker AT, Önder E, Sodan HT, Ünver H, Akansel G (2018) Neurotrophic factors and hippocampal activity in PTSD. PLoS One 13: e0197889

van Rooij SJH, Ravi M, Ely TD, Michopoulos V, Winters SJ, Shin J, Marin MF, Milad MR, Rothbaum BO, Ressler KJ, Jovanovic T, Stevens JS (2021) Hippocampal activation during contextual fear inhibition related to resilience in the early aftermath of trauma. Behav Brain Res 408:113282.

van Rooij SJH, Jovanovic T (2019) Impaired Inhibition as an Intermediate Phenotype for PTSD Risk and Treatment Response. Prog Neuropsychopharmacol Biol Psychiatry 89:435–445.

van Rooij SJH, Stevens JS, Ely TD, Hinrichs R, Michopoulos V, Winters SJ, Ogbonmwan YE, Shin J, Nugent NR, Hudak LA, Rothbaum BO, Ressler KJ, Jovanovic, T. (2018). The Role of the Hippocampus in Predicting Future Posttraumatic Stress Disorder Symptoms in Recently Traumatized Civilians. Biol Psychiatry 84:106–115.

van Rooij SJH, Stevens JS, Ely TD, Fani N, Smith AK, Kerley KA, Lori A, Ressler KJ, Jovanovic T (2016) Childhood Trauma and COMT Genotype Interact to Increase Hippocampal Activation in Resilient Individuals. Front Psychiatry 7:156.

Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP (2013) The PTSD Checklist for DSM-5 (PCL-5) – Standard [Measurement Instrument]. National Center for PTSD.

Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ (1996) Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biol Psychiatry 40:79–88.