Hippocampal Resting-State Functional Connectivity Forecasts Individual PTSD Symptoms: A Data-Driven Approach

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Abstract

Background: Posttraumatic Stress Disorder (PTSD) is a debilitating disorder and there is no current accurate prediction of who develops it after trauma. Neurobiologically, individuals with chronic PTSD exhibit aberrant resting-state functional connectivity (rsFC) between the hippocampus and other brain regions (e.g., amygdala, prefrontal cortex, posterior cingulate), and these aberrations correlate with severity of illness. Prior small-scale research ($n < 25$) has also shown that hippocampal-rsFC measured acutely after trauma is predictive of future severity using an ROI-based approach. While a promising biomarker, to-date no study has employed a data-driven approach to test whole-brain hippocampal-FC patterns in forecasting the development of PTSD symptoms.

Methods: Ninety-eight adults at risk of PTSD were recruited from the emergency department following traumatic injury and completed resting functional magnetic resonance imaging (rsfMRI; 8min) within 1-month; 6-months later they completed the Clinician-Administered PTSD Scale (CAPS-5) for assessment of PTSD symptom severity. Whole-brain rsFC values with bilateral hippocampi were extracted (CONN) and used in a machine learning kernel ridge regression analysis (PRoNTo); both a k-folds (k=10) and 70/30 testing vs. training split approach were used for cross-validation (1,000 iterations to bootstrap confidence intervals for significance values).

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Results: Acute hippocampal-rsFC significantly predicted CAPS-5 scores at 6-months (r=0.30, p=0.006; MSE=120.58, p=0.006; R^2=0.09, p=0.025). In post-hoc analyses, hippocampal-rsFC remained significant after controlling for demographics, PTSD symptoms at baseline, and depression, anxiety, and stress severity at 6-months (B=0.59, SE=0.20, p=0.003).

Conclusions: Findings suggest functional connectivity of the hippocampus across the brain acutely after traumatic injury is associated with prospective PTSD symptom severity.

Keywords

1. Introduction

Approximately 8–10% of American adults who experience a traumatic event will develop symptoms of post-traumatic stress disorder (PTSD), including hyperarousal, unwanted thoughts (e.g., flashbacks), and altered cognitive states(1). Among the most prevalent types of trauma is physical injury(2), with adults at heighted risk of developing symptoms (e.g., ~20% of survivors admitted to an emergency room meet criteria for PTSD diagnosis within one year).(3,4) While the overall understanding of PTSD etiology and its treatment continues to improve, implementation of therapeutic interventions early (e.g., in the weeks after trauma) yields the greatest benefits.(2,5,6) In order to provide early treatment, however, clinicians must be able to identify which individuals are at risk of developing PTSD.

Prior research demonstrates that pre-trauma risk factors such as sleep quality and presence of anxiety and depression increases the incidence of PTSD(7), while a number of pre- and peritraumatic factors, including those that are clinical (e.g., symptoms of distress) and biological (i.e., heart rate/blood pressure), can significantly add to the development of posttraumatic stress symptoms(8,9). The study of neural abnormalities qualified in the acute aftermath of trauma may also help identify those most at risk.(10–14) Much of this work has centered on the amygdala, involved in generation of negative affect.(10,15–18) However, the hippocampus, which is densely functionally and structurally connected to the amygdala, is responsible for the consolidation of fear memories(19) and is strongly implicated in PTSD.(20) Indeed, a fundamental feature of PTSD is atypical memory encoding and retrieval, particularly in the context of emotional memory(19,21–23), functions that are hippocampal-dependent(24). This is particularly true in the context of fear and extinction learning, whereby alterations in the hippocampus are often found in the context of trauma-related stimuli or general negative affect.(22,25) Notably, hippocampal aberrations frequently coincide with altered amygdala functioning.(22,25) Despite alterations in both regions(25), hippocampal functional discrepancies – but not always amygdala – are distinctly correlated with PTSD symptoms.(25) This suggests utility in explicitly studying hippocampal functioning as it relates to PTSD outcomes after trauma.

Prior theoretical models postulate altered stress hormone release via cortisol in individuals with PTSD has deleterious effects on the hippocampus, either by inducing cytotoxic effects(26) or impeding neuroplasticity.(27) Indeed, trauma-induced structural changes to the hippocampus may be associated with altered function.(28) Though prior research

shows instances of both hypo-(25,29) and hyper-engagement(30) of the hippocampus in response to negative and neutral stimuli as well trauma-specific reminders, these aberrations are associated with poor memory performance. Specifically, greater engagement of the hippocampus in response to negative words is associated with more false positives (e.g., misremembering novel stimuli).(30) Likewise, reduced activity in the hippocampus in response to trauma-specific stimuli is also associated with the presence of false alarms for trauma-related images.(25) Neurobiologically, this supports what has been demonstrated in behavioral studies of memory functioning for some time, namely that individuals with PTSD are less accurate compared to controls when recalling neutral(31), emotional(21), and episodic autobiographical information.(32) Such memory deficits have been posited to underlie the overgeneralization of fear as a cardinal symptom of PTSD(33), as the hippocampus contributes to both the extinction and/or regulation of fear in inappropriate contexts, by providing context-dependent processing.(22,34)

In addition, hippocampal aberrations in those with PTSD appear across various task-probes and in both affective(20) and cognitive domains(19), adding to its prevalence in this disorder. To this point, one of the most widely used techniques in studying the relationship between the hippocampus and PTSD is to quantify its functioning and associated connectivity during rest (e.g., when participants are not engaged in a task) and, indeed, individuals with chronic PTSD exhibit altered hippocampal functional connectivity at rest (hippocampal-rsFC). First, hippocampal-rsFC connectivity is altered with hubs of the default mode network (DMN), implicated in self-referential processing in the absence of task-demand. Specifically, those with PTSD show reduced connectivity of the hippocampus with the ventromedial prefrontal cortex (vmPFC)(35), medial prefrontal cortex(36), and PCC(37) compared to trauma exposed-controls. Other work has found evidence of *greater* integration of the hippocampus with the DMN(38) and greater integration of the hippocampus with regions of the salience network (SN), which is involved in the detection of salient stimuli.(39) This suggests that altered processing of learned fear (subserved by the hippocampus) may be related to differences in internally focused (e.g., DMN) and externally focused thought (e.g., SN) (39) in those with PTSD. Second, although hippocampal-rsFC with nodes of the DMN is atypical in individuals with PTSD *and* generalized anxiety disorder (GAD) compared to healthy controls, this effect is driven by those with PTSD as the primary diagnosis. (40) Finally, several studies demonstrate that hippocampal-rsFC correlates with individual variability of PTSD symptoms.(41,42) Decreased hippocampal-rsFC with the amygdala(43–45), mPFC(35), and PCC(37,46), while hippocampal-rsFC with the vmPFC and dorsolateral prefrontal cortex (dlPFC)(47) are all significantly related to PTSD severity. Combined, this research demonstrates aberrant hippocampal-rsFC in those with PTSD compared to controls and that this characteristic distinguishes PTSD from other internalizing disorders(40) while meaningfully correlating with severity of the disorder.

Although cross-sectional associations with symptoms is informative, the hippocampus may also be a critical brain region important for disease onset and trajectory. A consistent, though not flawless(48–50) biomarker of the development of PTSD after trauma is smaller hippocampal volume *pre*-trauma.(12,17,51–53) An increasing body of work also suggests the hippocampus may undergo early changes in response to trauma (e.g., within days and up to one year following trauma exposure) that can be measured via hippocampal-

rsFC and directly related to PTSD symptom progression.(46,54,55) Greater acute post-trauma hippocampal-rsFC with the amygdala(54), PCC(55), and between hippocampal subfields(46) is a significant predictor of less PTSD symptoms up to four(46) and six months after trauma exposure.(54,55) Other work demonstrates greater acute post-trauma PFC connectivity with an "arousal network" – defined in part by the hippocampus – predicts less PTSD severity three months after trauma.(56) Importantly, PTSD is frequently co-morbid with major depressive depression (MDD)(57), with multiple overlapping symptoms characterizing both disorders.(58) Yet, to our knowledge, the above studies did not test whether hippocampal connectivity measured acutely post-trauma forecasts future PTSD severity while accounting for co-morbid symptoms of depression.

The above work implies value of hippocampal-rsFC for the prediction of PTSD and that this relationship is not dependent on connectivity with a single brain region. Thus, in contrast to singular region approaches, machine-learning methods offer an opportunity to explore the most useful disorder-specific neural patterns across the *entire* brain without the constraints of traditional univariate schemes.(59) Multivariate variate pattern analysis (MVPA) offers such an innovative approach towards forecasting mental health outcomes. In recent years, MVPA has been applied to understanding the neural correlates of PTSD(15,60,61), MDD(62–64), and other disorders.(65) Briefly, this machine learning approach tests whether whole-brain distributed rsFC patterns are useful in predicting individual symptoms.(66) By analyzing neural spatially-distributed activation, MVPA can be used to "decode" the brain and identify information (i.e., future PTSD symptom severity) that is represented in voxels throughout the whole brain, with voxels representing either activation during task-based activities, or connectivity with another part of the brain (e.g., hippocampus).(66–69) Past MVPA approaches have used hippocampus whole-brain connectivity to discriminate when individuals with PTSD are engaged in trauma recall versus neutral imagery.(60) Other machine learning techniques have shown that mean volume reduction in the hippocampus contributes to accurate classification of those with PTSD from controls (accuracy: 69%, specificity: 81%).(70) Additionally, a machine learning classifier investigation found that amygdala-hippocampal structure via tract strength contributed to accurate prediction of trauma-exposed versus trauma-naive individuals.(71) Thus, patterns of hippocampal-based activation(60) and hippocampal structure(70) can significantly predict trauma history, PTSD symptoms, and unique features of the disorder. However, to our knowledge, MVPA has never been applied to examine the utility of hippocampal-rsFC to forecast individual PTSD symptom severity.

In this study, we employed MVPA to test whether acute (i.e., within one-month post-injury) hippocampal-rsFC patterns forecasted participants' future (i.e., six-months post-injury) clinician-assessed PTSD symptom severity in a large, heterogenous sample of PTSD at-risk participants. We assessed PTSD symptoms using the Clinician-Administered PTSD Scale for DSM-5(CAPS-5), considered to be the "gold-standard" assessment of PTSD.(72,73) Previous MVPA work in PTSD(15,61) has employed less reliable measures (i.e., self-report measures) of PTSD, such as the PTSD Checklist. Based on findings from previous studies, we hypothesized that post-injury hippocampal-rsFC would significantly forecast individual PTSD total symptom severity at six-months post-injury and, importantly, that the prediction

would still be significant in a regression model adjusting for six-month general depression, anxiety, stress scores and baseline PTSD symptoms.

2. Material and Methods

2.1. Participants

Traumatically-injured adults were recruited from a Level 1 Trauma Center either directly from the Emergency Department (ED) or by phone following ED discharge. Participants were eligible if they: a) were between the ages of 18–60, b) were English speaking, c) met the Diagnostic and Statistical Manual-5th edition (DSM-5) Criterion A for a PTSD diagnosis, and d) exhibited a greater risk of developing PTSD based on a minimum score of 3 (out of 5) on the Predicting PTSD Questionnaire.[74] Participants were excluded if they: a) experienced a moderate or severe head injury as the result of their trauma based on a score of > 13 on the Glasgow Coma Scale[75,76], b) suffered a spinal cord injury with neurological deficit, c) were admitted to the ER as the result of intentional self-inflicted injury, d) exhibited severe vision or hearing impairments, e) had a history of psychotic or manic symptoms or were currently taking antipsychotic medications, f) a history of clear substance abuse, g) on police hold following their traumatic injury, or h) were MRI incompatible based on the following: presence of ferromagnetic material in the body, claustrophobia, inability to lie still for two hours, or either currently pregnant or trying to become pregnant. Exclusion criteria was assessed via self-report during the screening process and additionally via a review of medical records for the presence of diagnostic codes. All participants provided written consent and all study procedures were approved by the local Institutional Review Board. Participants were compensated for their time and all procedures complied with the Helsinki Declaration.

2.2. Procedure

Upon enrollment, participants completed an 8-minute rsfMRI scan within one month of their traumatic injury. At that visit (henceforth referred to as 'baseline') they also completed a number of demographic and clinical assessments, including the PTSD Checklist for DSM-5 (PCL-5).[77] The PCL-5 is a 20-item self-report measure of post-traumatic stress symptoms with good internal consistency (Cronbach's alpha = 0.94), convergent validity ($r > 0.75$), and test-retest reliability ($r = 0.92$).[78] Six months later, participants returned for a follow-up visit, at which time they completed the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[79] with a trained research staff member. The CAPS-5 is considered a "gold-standard" assessment of PTSD, exhibits high internal consistency ($\alpha = .88$) and good test-retest reliability (ICC = .78).[80] An internal reliability check on the CAPS-5 was completed for this study across two separate raters for 20% of CAPS-5 completed at six months. Results demonstrated excellent agreement among raters (kappa = 0.83, $p < 0.001$) and excellent reliability between total symptom severity scores (ICC = 0.96 [95% CI: 0.93–0.98]).

In addition to the CAPS-5, participants completed the Depression Anxiety and Stress Scales (DASS-21) at the six month visit for self-reported assessment of general depression, anxiety,

and stress severity(81). Each of the depression (α = .81), anxiety (α = .89), and stress (α = .78) scales of the DASS-21 have been found to have excellent internal consistency.(82)

2.2.1   Resting State fMRI Acquisition—During the rsfMRI scan participants viewed a white crosshair displayed on a black background and were instructed to keep their eyes open. Scanning was performed on a 3.0 Tesla short bore GE Signa Excite MRI system at the Medical College of Wisconsin. Functional T2*-weighted echoplanar images (EPI) were collected in a sagittal orientation with the following parameters: repetition time (TR)/echo time (TE)=2000/25ms; FOV=22.4mm; matrix=64×64; flip angle=77°; slice thickness=3.5mm; voxel size=3.5 × 3.5 × 3.5mm; # slices = 41; volumes = 192. A high-resolution T1-weighted anatomical image was also acquired for co-registration with the following parameters: TR/TE=8.2/3.2ms; FOV=240mm; matrix=256×224; flip angle=12°; voxel size=0.9375 × 1.071 × 1mm, # slices = 150.

2.3.   Data Analysis

2.3.1.   Image Preprocessing—Individual functional images were analyzed using the CONN functional connectivity toolbox(83) and preprocessed according to standard procedures. Briefly, images underwent spatial realignment using the SPM12 *realign and unwarp* procedure(84) with all scans referenced to the first image and estimated motion parameters calculated across six variables representing three translation (displacement) parameters and three rotation parameters. Temporal misalignment was corrected using slice-time correction.(85) As small head movements can cause spurious noise and distance-dependent changes in signal correlations(86,87), frame-wise displacement (FD) was computed to rule out confounding effects of motion. Volumes with FD > 0.2 mm (plus 1-back and 2-forward neighboring volumes) were 'scrubbed' (e.g., removed from analysis). Participants were excluded if more than 25% of the frames were scrubbed. In addition, subjects with cumulative movement > 3 mm or 3 degrees of rotation were identified for removal from analysis. Structural segmentation and normalization were done to classify data into grey matter, white matter, and cerebrospinal fluid (CSF) through the estimation of the posterior tissue probability maps (TPMs) in SPM12.(88) Images were then normalized to the Montreal Neurological Institute (MNI) template and smoothed with a 4 mm^3 Gaussian kernel.(89) To isolate rsfMRI signal, resulting data were bandpass filtered at 0.01– 0.09 Hz, while signal from cerebrospinal fluid, white matter, and motion realignment parameters were entered as regressors of no-interest to control for these effects during scanning.

2.3.2.   Pattern Recognition Analysis—Two whole-brain hippocampal-rsFC maps were computed for each subject at the first-level using CONN, one representing connectivity with the right hippocampus and one with the left hippocampus. Each map's voxels represented a Fisher-transformed bivariate correlation coefficient between the respective seeds' (e.g., right and left hippocampi) BOLD timeseries and every other voxel's BOLD timeseries. The right and left hippocampi were defined using the Anatomical Automatic Labeling (AAL)-defined mask from the SPM toolbox.(90,91)

Both maps were subsequently used as features in a multivariate kernel ridge regression (KRR) using the PRoNTo toolbox (http://www.mlnl.cs.ucl.ac.uk/pronto/).(92) KRR is a

machine learning technique and a form of linear ridge regression (sum of squares) with the addition of a kernel function. Ridge regression introduces bias in order to improve model fit and accuracy of forecasted predictions. Extending this approach, KRR adds a function based on the "kernel trick", whereby a kernel is used to improve model fit by operating in feature space. KRR is often considered an improvement on regression-based models for prediction as it offers a more efficient way to transform the data without the need to compute coordinates in a higher dimensional space.(93)

Each hippocampal-rsFC map served as its own feature (features: $n = 2$) and was provided for each individual subject while feature selection was constrained to voxels inside the brain through the use of a standard binary mask(92). In the calculation of features, a linear kernel was used with a square matrix of dimensions N x N, where the kernel reflected a similarity measure between each participant, called the dot product. We did not use a second-level mask to constrain feature selection by a subset of voxels; instead, all voxels within the brain (representing connectivity with the respective hippocampal seed region) were used for model prediction. Model prediction using the KRR approach was then computed and generalizability estimated using two different approaches. First, to utilize the entire sample, we used a k-folds ($k = 10$) approach for cross-validation. The k-folds approach for cross-validation has been used previously in machine learning investigations involving those with PTSD(94) and may be superior to the use of training versus test datasets for this purpose when sample sizes are considered small by machine learning standards. Importantly, cross-validation ensures that the model is generalizable and prevents overfitting. Identical to past studies(15), features (i.e., L and R hippocampal-rsFC maps) were first mean centered using the training data (9-folds; 90% of dataset). In addition to this approach, we also split our dataset into a training set (~70% of sample) and a testing set (~30%) and used a k-folds approach where $k = 1$ to train on the 70% sub-sample and subsequently test the model performance on the 30% sub-sample. In both approaches, the performance of the model was characterized using several metrics, including the (cross-validated) Pearson correlation coefficient (r), mean squared error (MSE) and the coefficient of determination (R^2) between model-estimated CAPS-5 and the true CAPS-5 scores. Significance values for prediction scores were obtained using permutation testing across 1,000 iterations, a necessary step when dealing with large neuroimaging datasets that violate the assumption that data is independently and identically distributed. The choice for 1,000 permutations was based on current recommendations(95) and identical to prior machine learning MVPA publications using neuroimaging data.(15,61)

Results of the model were also viewed through the calculation of weights for each voxel as a colormap, whereby warmer colors reflected voxels that increased model prediction by a value of the features (e.g., hippocampal-rsFC) and cooler colors reflected voxels that decreased model prediction by a value of the features, assuming all other voxels are fixed. That is, each voxel's contribution to the model performance was visualized. Post-hoc averaging of weight values by individual brain regions was also done during this step(96), although we did not constrain weight contribution to its average within brain regions for the calculation of the model. Here, post-hoc averaging of weight values was done only for illustrative purposes, similar to other published accounts(15,61,97), as all voxels contributed to model performance and it is inaccurate to single out the predictive utility of one region.

(98) For averaging of weight values by brain region, we used the AAL atlas, resulting in the averaged weight values for $N = 117$ brain regions.

3. Results

3.1. Participants

A total of $N = 139$ participants was initially recruited for this study. Of this, 31 participants were excluded from analysis for the following reasons: a) lost to follow-up ($n = 12$), b) excess motion during rsfMRI defined as > 25% volumes lost in scrubbing and/or 3 mm movement in any one direction ($n = 28$), or c) alignment problems in reconstruction of imaging data ($n = 1$). This left a final sample of $N = 98$.

Participants completed their baseline appointment between 6–33 days after injury (M = 18.57 days, SD = 5.51 days) and their follow-up appointment between 5–8 months after injury (M = 6.07 months, SD = 0.43 months). Mechanism of injury varied across the sample but consisted primarily of survivors of motor vehicle crashes (67%). The remaining injuries were classified as: assault (16%), crush injuries (<5%), pedestrian injuries (<5%), dog bites (<5%), falls (<5%), gunshot (<5%), domestic violence (<5%), sexual assault (<5%), and bicycle accident (<5%; exact percentage is not included to ensure participant confidentiality). Complete participant demographics are reported in Table 1.

3.2. PTSD Symptoms

At baseline, PTSD severity measured by the PCL-5 ranged from 0–73 (M = 25.76, SD = 17.41). At six months, PTSD severity as measured by the CAPS-5 ranged from 0–63 (M = 11.98, SD = 11.53), indicating that six months after injury participants ranged from asymptomatic to severe PTSD symptomatology(99).

3.3. MVPA Results

Using the full-sample in cross-validation, model results demonstrated that baseline whole-brain hippocampal-rsFC significantly predicted CAPS-5 scores at six months ($r = 0.30$, $p = 0.006$; mean squared error = 120.58, $p = 0.006$; $R^2 = 0.09$, $p = 0.025$). Results were the same when using a training ($n = 68$) vs. testing ($n = 30$) set for model validation ($r = 0.46$, $p = 0.002$; mean squared error = 217.38, $p = 0.003$; $R^2 = 0.21$, $p = 0.007$). As results of model fit did not change based on which cross-validation method was used, the remaining results reflect when the full sample ($N = 98$) was used in cross-validation. Together, this suggests that the model prediction was an accurate fit (based on significant MSE) and that actual CAPS-5 scores (i.e., the targets in our regression) were well correlated with our predicted values based on model fit (given a significant R^2). Spatial distribution of color-coded model weights for each voxel are depicted in Figure 1. Similar to other published MVPA studies(15,61,97), KRR-derived weights constrained by brain region for the top 10% of regions that contributed to model prediction are reported in Table 2.

Predicted targets based on model fit were subsequently extracted for use in post-hoc analyses to examine this relationship further while controlling for select covariates(100). We controlled for covariates in this fashion given that the addition of covariates within the model

prediction is applied to the linear kernel, which is limited in removing the linear confound for each effect for each voxel without assessing the effect of the covariate on the pattern of voxels (e.g., at the multivariate level). Extraction of the predicted model values alternatively allowed us to examine the significance of the multivariate model fit controlling for univariate factors. Here, predicted targets were used in a hierarchical linear regression using SPSS (Version 26) to examine the strength of the relationship between predicted and actual targets controlling for gender (dichotomous variable; reference = 0 [male]), mean-centered age, mean-centered time since injury at baseline, mean-centered time since injury at six months, mean-centered PCL-5 scores at baseline, and mean-centered DASS-21 depression, anxiety, and stress ratings at six months entered into Step 2 of the model. In addition, for controlling for differences in demographics and timing in the administration of measures, this allowed for the control for the presence of PTSD stress symptoms at baseline (i.e., the time of rsfMRI data collection), and to test for specificity in the relationship between hippocampal-rsFC and PTSD symptoms. Assumptions of the linear model were met, such that residuals were homoscedastic and there were no issues of multicollinearity (VIF < 4.5).

Results demonstrated that the relationship between predicted (based on model fit) and actual CAPS-5 scores remained significant controlling for these factors (B = 0.59, SE = 0.20, p = 0.003). Results of the post-hoc hierarchical linear regression are reported in Table 3; Figure 2 depicts the partial regression relationship between actual CAPS-5 scores (y-axis) plotted against predicted CAPS-5 scores based on the MVPA algorithm (x-axis) controlling for covariates.

4. Discussion

To assess the utility of whole-brain hippocampal-rsFC to forecast future PTSD symptom severity, adult survivors of a traumatic injury completed a rsfMRI scan acutely post-injury (within one month) and a structured clinical interview evaluating PTSD symptoms approximately six-months post-injury. Results demonstrated that hippocampus-rsFC across the whole brain was a significant predictor of future PTSD severity, even after controlling for gender, PTSD self-reported symptoms at baseline, and general depression, anxiety, and stress symptoms as they were reported at follow-up. That is, findings suggest that functional integration of the hippocampus across the brain acutely after traumatic injury is a promising biomarker for prospective PTSD severity, and that this relationship is specific to PTSD when compared to general depression, anxiety, and stress symptom development.

Results support the use of data-driven, MVPA approaches for the prediction of psychiatric illness(62–65), including PTSD symptom severity(15,61,101) or dichotomous PTSD diagnosis.(102) Further, the strength of the relationship we discovered between predicted and actual symptom severity based on the model performance (r = 0.30) was similar to previous MVPA approaches that have predicted PTSD outcomes using other seed regions (e.g., r's range from 0.28(103) to 0.46(15)). Thus, akin to other studies investigating brain-based biomarkers using machine learning(15,61,101,102), hippocampal-rsFC has a moderate effect size in forecasting individual PTSD psychopathology.

Importantly, our findings support the recommendation to explore hippocampal-rsFC across the entire brain, rather than narrowing the focus on *a priori* selection of its connectivity with a select number of brain regions or networks. Increasingly, studies demonstrate the value of studying patterns of voxel-to-voxel activation in those with PTSD. For instance, Cisler and colleagues found voxel-to-voxel patterns of activation during trauma memory recall was a better predictor of PTSD diagnosis than the traditional use of ROI-to-ROI differences in activation(60), while other research shows that whole-brain connectivity is a better predictor of PTSD in combat veterans than 32 non-imaging markers (e.g., behavior, clinical symptoms).(104) Similarly, Suo and colleagues recently demonstrated whole-brain connectivity across 268 ROIs within the brain was able to significantly "predict" cross-sectional PTSD symptom severity in survivors of an earthquake(101). In this latter study, connections between the occipital lobe and cerebellum as well as connections of limbic regions (including hippocampus) with the occipital lobe and cerebellum were the primary connections that successfully predicted PTSD severity.(101) Notably, connections between these brain regions, with exception of the traditional "limbic structures," are rarely studied in the context of PTSD. Finally, model-fits determined by whole-brain resting-state average amplitude of low frequency fluctuations have been shown to be better predictors of PTSD symptom severity than constraining the feature-selection with a mask encompassing the bilateral PFC, amygdalae, and hippocampi.(61) Indeed, in addition to hippocampal connectivity with regions involved in fear generation (i.e., amygdala) as well intra-hippocampal connectivity (including with the parahippocampal gyrus), we also found that hippocampal-cerebellum rsFC contributed greatly to model fit based on our post-hoc review of the top 10% of regions that contributed to model performance. Structural abnormalities of the cerebellum, a region traditionally associated with motor coordination and movement-related learning(105), have recently been indicated as a risk factor for common cognitive and affective disorders across categorial diagnoses(106), and recent research highlights that cortico-cerebellum circuitry may be important for integration and coordination of affective functioning that is related to psychiatric illness.(107) Taken together, this suggests a need for revisiting the traditional view of PTSD as a disorder specific to fronto-limbic aberrations.(108)

The present findings have important treatment implications. First, our study assessed hippocampal-rsFC within weeks of trauma exposure as a predictor of severity of symptoms months later. This research demonstrates that early screening for risk for PTSD diagnosis may benefit by examining neurobiological features such as hippocampal-rsFC early in disease progression. Second, unlike other studies, we explored the prediction of PTSD symptoms controlling for general depression, anxiety, and stress severity. Thus, results suggest that although PTSD is comorbid with depression and anxiety disorders(109) and prior studies have questioned the utility of hippocampal volume as a unique biomarker of PTSD(49), PTSD may still be qualified by unique neurobiological features, such as altered whole-brain hippocampal-rsFC. Finally, given the use of a continuous PTSD measurement, findings demonstrate that the prediction of continuous PTSD severity that includes sub-threshold presentation remains crucial, as it also causes clinically significant impairments(110) and represents a significant subset of trauma-exposed adults.(111)

The present study is not without limitations. First, despite the fact that this sample was comprised of individuals who experienced varied mechanisms of injury, the majority of our sample (67%) were admitted to the emergency department following motor vehicle crash. Thus, findings may not be generalizable to individuals who have developed PTSD resulting from other trauma types. In addition, the use of a Glasgow Coma Scale score of > 13 during screening means that some individuals may have had a mild traumatic brain injury (mTBI). Although this score suggests that the mTBI injury is minor(75,76), future research on the impact of mTBI on rsFC should be examined. Although our sample is moderately-large for neuroimaging studies and keeping with other machine learning investigations in PTSD using fMRI data (which used sample sizes ranging from $N =$ 40(112) to $N =$ 186(113)), our sample is considered small (though still acceptable based on $n = 80$ cut-off to reduce error below 0.01) for machine learning approaches that utilize biomedical data.(114) As depression prognosis was a secondary interest in the present study, we relied on a self-reported measure of depression symptoms at six months through the DASS-21. Thus, it will be helpful to re-investigate these findings with the use of more robust measures of depression (e.g., CESD-R(115)). Finally, although significance of the model was retained after controlling for univariate confounds in post-hoc regression, we were unable to adequately account for multivariate confounding, or the effect of a confound on the pattern of voxels, which is a known limitation of the present analysis.

Despite these limitations, several important conclusions can be drawn from our findings. First, this is one of the only published studies to-date that has examined hippocampal-rsFC in the acute aftermath of traumatic injury as a *prospective* predictor of PTSD symptom development and using a large sample size (prior accounts have used samples of $n <$ 25(46,55) or reported preliminary data in conference proceedings(54)). In addition, this is the only study to our knowledge that employs a multivariate, machine-learning analytic approach to the question of hippocampal-rsFC and PTSD prediction. Results provide further rationale for not restricting the study of the biological underpinnings of PTSD to limbic structures. Given the multitudinous role of the hippocampus in both memory formation and fear regulation, in addition to the constellation of PTSD symptoms spanning domains of memory alterations and altered arousal, results support the conclusion that hippocampal distributed connectivity across the brain may be consequential for understanding PTSD prognosis in trauma survivors.

Acknowledgments

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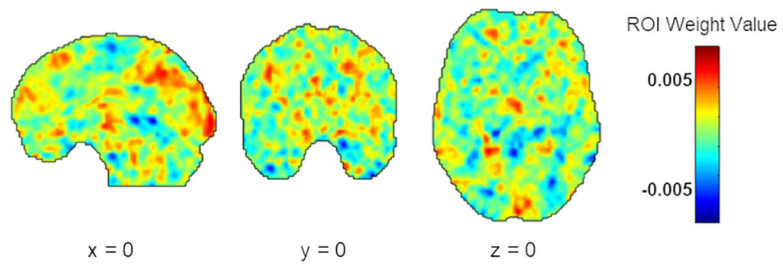
Figure 1.
Results of the KRR analysis depicting computed weight values in arbitrary units for each voxel across the entire brain. Warmer colors indicate that these regions positively contributed to model performance. In contrast, voxels with low weight values, represented by cooler colors, indicate weight values that negatively contributed to model performance (e.g., push it toward decreased prediction). *Note:* **KRR**, kernel ridge regression.
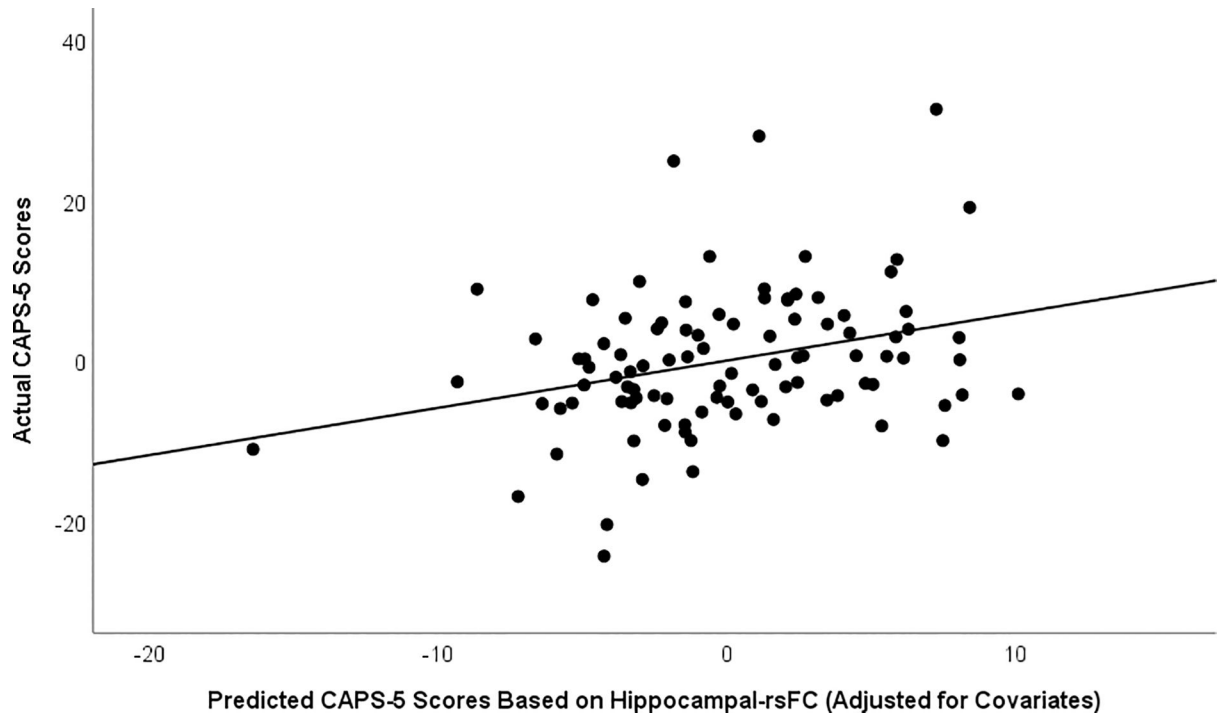
Figure 2.
Significant relationship between actual and predicted CAPS scores based on the MVPA algorithm controlling for all covariates (B = 0.59, SE = 0.20, *p* = 0.003).

Table 1.

Sample Demographics (N = 98)

	M (SD)
Age	33.52 (10.30)
Education (years)	14.92 (2.39)
PCL-5 at baseline	25.76 (17.41)
DASS-21: Depression at six months	7.38 (9.06)
DASS-21: Anxiety at six months	7.53 (8.07)
DASS-21: Stress at six months	10.70 (9.07)
CAPS-5 at six months	11.98 (11.53)
	n (%)
Gender (Female)	53 (54%)
Ethnicity (Hispanic or Latino)	9 (9%)
Race	
Asian	< 5 (< 5%)
Black or African American	54 (55%)
White	32 (33%)
More than one race	5 (5%)
Unknown or not reported	6 (6%)

Note. **PCL-5**, PTSD Checklist for DSM-5; **DASS-21**, Depression Anxiety Stress Scales; **CAPS-5**, Clinician-Administered PTSD Scale. Small sample sizes for select racial groups are reported as < 5% to avoid participant identification; thus, cumulative percentage surpasses 100% as reported here.

Table 2.

Top 10% of Model Weights per Regions-of-Interest

Region-of-Interest	Laterality	Direction	Weight (%)	Size (voxels)	Expected Ranking	MNI Coordinates		
						x	y	z
Cerebellum	L	Negative	1.39	1140	116.81	−14	−44	−28
Cerebellum Crus	R	Negative	1.37	2026	116.12	36	−70	−30
Amygdala	R	Positive	1.28	240	114.70	26	0	−16
Cerebellum Crus	L	Negative	1.21	2239	113.39	−36	−70	−28
Hippocampus	R	Negative	1.20	951	112.82	28	−18	−12
Cerebellum	R	Negative	1.18	316	111.33	32	−72	−46
Cerebellar Vermis	Midline	Negative (L)	1.16	669	110.50	2	−52	−6
Parahippocampal Gyrus	L	Positive (R), Negative (L)	1.16	985	110.24	−22	−16	−22
Cerebellum Crus	R	Negative	1.15	1668	109.51	28	−78	−40
dmPFC	R	Positive	1.09	1904	107.27	8	52	32
Heschl's Gyrus	L	Positive (L), Negative (R)	1.08	224	106.04	−42	54	10

Note. **MNI**, Montreal Neurological Institute; **dmPFC**, dorsomedial prefrontal cortex; **L**: left; **R**: right. Reported regions represent top 10% of regions based on weight. Direction indicates whether the connectivity pattern was positive (greater connectivity) or negative (reduced connectivity). When differential connectivity patterns were observed, the laterality of the seed hippocampus is included in parentheses. Weight is determined by the contribution of that region divided by the total contribution of all regions and displayed as a percentage. Expected ranking reflects how stable the ranking of each region is across folds. Although only the top 10% of model weights per regions-of-interest are displayed here, all voxels contributed to model fit and weights were averaged by brain region in a post-hoc fashion for interpretability of model outcome.

Table 3.

Post-hoc Hierarchical Linear Regression

Variable	Actual CAPS-5 Scores at Six Months					
	B	SE	β	t	p-value	
Step 1						
Intercept	12.03	1.108		10.862	< 0.001	***
Target CAPS-5 based on model prediction	**0.81**	**0.23**	**0.34**	**3.51**	**0.001**	**
Step 2						
Intercept	10.59	1.41		7.53	0.000	
Target CAPS-5 based on model prediction	**0.59**	**0.20**	**0.25**	**3.02**	**0.003**	**
Gender	2.61	1.98	0.11	1.32	0.192	
Age	0.05	0.10	0.05	0.55	0.586	
Time since injury at baseline	2.35	5.56	0.04	0.42	0.674	
Time since injury at six months	−2.45	2.22	−0.09	−1.10	0.273	
PCL-5 at baseline	0.08	0.06	0.12	1.26	0.212	
DASS-Depression at six months	0.10	0.20	0.08	0.50	0.621	
DASS-Anxiety at six months	0.69	0.23	0.48	2.97	0.004	**
DASS-Stress at six months	−0.01	0.20	−0.01	−0.05	0.957	

Note. **CAPS-5**=Clinician-Administered PTSD Scale; **PCL-5**=PTSD Checklist-Civilian Version; **DASS**=Depression Anxiety Stress Scales

***
$p < 0.001$

**
$p < 0.01$; $\underline{N = 98}$.