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Less Is More: Smaller Hippocampal Subfield Volumes Predict Greater Improvements in Posttraumatic Stress Disorder Symptoms Over 2 Years

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Posttraumatic stress disorder (PTSD) is a heterogeneous disorder, and symptom severity varies over time. Neurobiological factors that predict PTSD symptoms and their chronicity remain unclear. This study investigated whether the volume of the hippocampus and its subfields, particularly cornu ammonis (CA) 1, CA3, and dentate gyrus, are associated with current PTSD symptoms and whether they predict PTSD symptom changes over 2 years. We examined clinical and structural magnetic resonance imaging measures from 252 trauma-exposed post-9/11 veterans (159 with Time 1 PTSD diagnosis) during assessments approximately 2 years apart. Automated hippocampal subfield segmentation was performed with FreeSurfer Version 7.1, producing 19 bilateral subfields. PTSD symptoms were measured at each assessment using the Clinician-Administered PTSD Scale–IV (CAPS). All models included total intracranial volume as a covariate. First, similar to previous reports, we showed that smaller overall hippocampal volume was associated with greater PTSD symptom severity at Time 1. Notably, when examining regions of interest (CA1, CA3, dentate gyrus), we found that *smaller* Time 1 hippocampal volumes in the bilateral CA1-body and CA2/3-body predicted *decreased* PTSD symptom severity at Time 2. These findings were not accounted for by combat exposure or treatment history. Additionally, both Time 1 CA1-body and CA2/3-body volume showed unique associations with changes in avoidance/numbing, but not with changes in reexperiencing or hyperarousal symptoms. This supports a more complex and nuanced relationship between hippocampal structure and PTSD symptoms, where during the posttrauma years bigger may not always mean better, and suggests that the CA1-body and CA2/3-body are important factors in the maintenance of PTSD symptoms.

Keywords: posttraumatic stress disorder, veterans, hippocampus, cornu ammonis 1, cornu ammonis 3

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Posttraumatic stress disorder (PTSD) is a disabling condition that develops after exposure to a highly distressing traumatic event and is characterized by reexperiencing, avoidance, numbing, negative alterations to cognition and mood, and hyperarousal symptoms. PTSD has been associated with heterogeneous symptom trajectories (Andersen et al., 2014; Bonanno & Mancini, 2012; Bonanno et al., 2012; Dickstein et al., 2010; Lee et al., 2020; Orcutt et al., 2004). For example, in a combat-exposed sample with and without PTSD, Karstoft et al. (2013) identified four distinct trajectories: chronic (persistent symptoms), recovering (gradually

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declining symptoms), delayed onset (increase in symptoms following a delay), and resilience (initial low level of symptoms that remain low or subside). Though studies have looked at predictors of PTSD symptom changes (e.g., inhibitory control, DeGutis et al., 2023; depression, Sripada et al., 2017; alcohol use, Lee et al., 2020; executive functioning, Jagger-Rickels et al., 2022), factors that predict PTSD symptom changes require additional characterization. One model of PTSD suggests that variations in certain brain structures and functions may represent neurobiological vulnerabilities, predating the trauma or development of PTSD (e.g., Admon et al., 2013). However, less is known about how neurobiological vulnerabilities relate to PTSD symptom changes over a broader timescale (i.e., many years after the trauma). Notably, risk factors for the development of PTSD have often been shown to dissociate from factors involved in maintaining PTSD (Brewin, 2005; Johnson & Thompson, 2008; Meyer et al., 2019; Schnurr et al., 2004). The goal of the present study was to better characterize the neurobiological mechanisms that predict changes in PTSD symptoms over time years after trauma.

One potential neurobiological candidate to predict PTSD symptom changes is the structural integrity of the hippocampus. Several meta-analyses, including a large-scale consortium meta-analysis, have reported smaller overall hippocampal volume in those diagnosed with PTSD and with greater PTSD symptom severity (Karl et al., 2006; Kitayama et al., 2005; Kühn & Gallinat, 2013; Logue et al., 2018; O'Doherty et al., 2015; Woon et al., 2010, though see Smith, 2005). The hippocampus has been consistently implicated in fear-related learning/extinction processes and generalization of learning (Bremner et al., 2005; Liberzon & Sripada, 2007; Milad et al., 2009, 2007; Pitman et al., 2012; Rougemont-Bücking et al., 2011; L. M. Shin & Liberzon, 2010), and deficits in these processes have been shown to play an integral role in the development and maintenance of PTSD (Milad et al., 2008; Orr et al., 2000; Rauch et al., 2006; Verfaellie & Vasterling, 2009). Studies have demonstrated that a smaller hippocampus is a precursor or risk factor for the development of PTSD (Gilbertson et al., 2002; Kremen et al., 2012; Pitman et al., 2006) rather than resulting from PTSD symptoms. Only a few studies have investigated the relationship of the hippocampus with change in PTSD symptom severity over time, and the majority of studies have focused on treatment-related changes in hippocampal volume (Butler et al., 2018; Levy-Gigi et al., 2013; Suarez-Jimenez et al., 2020; Rubin et al., 2016; Zilcha-Mano et al., 2023; van Rooij et al., 2015; Vermetten et al., 2003). A few of these studies showed that greater overall hippocampal volume is associated with better treatment response (Suarez-Jimenez et al., 2020; Rubin et al., 2016; Zilcha-Mano et al., 2023), and some evidence suggests that PTSD treatment can increase the volume of the hippocampus (e.g., Butler et al., 2018; Levy-Gigi et al., 2013), though this was not found in van Rooij et al. (2015). The drawbacks of these studies are that they have relatively small samples ($N \leq 76$), have focused on short-term treatment rather than the long-term, non-treatment-related changes in PTSD, and have examined the hippocampus as a single entity.

The hippocampal formation is an anatomically complex structure composed of several functionally distinct subfields. Some of the most well-studied subfields include the dentate gyrus (DG), subiculum, parasubiculum, and cornu ammonis (CA) 1–4. The DG is involved in pattern separation, a process by which features are distinguished from each other at the time of encoding to store similar memories as distinct events (Bakker et al., 2012; Leutgeb et al., 2007; Schmidt et al., 2012; Yassa & Stark, 2011). Pattern separation deficits have been associated with fear overgeneralization (Besnard & Sahay, 2016; Kheirbek et al., 2012; Lange et al., 2017), which occurs in PTSD (Dunsmoor & Paz, 2015; Dymond et al., 2015; Morey et al., 2015). The CA3 is involved in pattern completion or the ability to recall events in response to partial features and has been associated with contextual fear conditioning (Leutgeb et al., 2007), another process implicated in PTSD (Milad et al., 2008; Rougemont-Bücking et al., 2011). The CA1 has been associated with the encoding and retrieval of context-dependent memories (Tsien et al., 1996; Akbari et al., 2006), including contextual fear conditioning (Daumas et al., 2005; Zamorano et al., 2018), which is a core impairment in models of PTSD (Dillon et al., 2008; Furini et al., 2014; Tronson et al., 2009). Given previous work pointing to deficits in episodic and contextual memory and fear learning/extinction in PTSD (Milad et al., 2008; Morey et al., 2015; Rauch et al., 2006; Verfaellie & Vasterling, 2009),

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The data and analytic code that support the findings of this study will be made available in an Open Science Framework repository upon approval by the VA Boston Healthcare Institutional Review Board (IRB). The present study was not preregistered. A version of this article was uploaded to psyArXiv on June 1, 2023, at https://psyarxiv.com/qtfa5. This work was presented at the 2022 Biological Psychiatry Conference (Vol. 91: 9, S357–S358).

The authors report how they determined their sample size, all data exclusions, manipulations, and measures in the study. There was no prior dissemination of this data. The study design and analysis plan were not preregistered. Raw data files are available following standard data sharing protocols at the VA Boston IRB. Computer syntax is available through SPSS and R upon request. Please contact Joseph DeGutis at degutis@wjh.harvard.edu. The VA Boston Healthcare System IRB approved this study (No. 2354, Translational Research Center for Traumatic Brain Injury and Stress Disorders: Human Characterization Core B), written consent was obtained from all participants, and research was conducted in accordance with the Declaration of Helsinki.

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it is plausible that the DG, CA3, and CA1 all play a role in the development and maintenance of PTSD. Consistent with this notion, the handful of studies investigating hippocampal subfields in those with PTSD have found, compared to controls, smaller volume in the DG (Hayes et al., 2017; Postel et al., 2021), CA3 (Postel et al., 2021; Wang et al., 2010), and CA1 (Chen et al., 2018; Postel et al., 2021). However, to our knowledge, only one study by Weis et al. (2021) has investigated how subfields relate to PTSD symptoms over time, finding no significant associations between hippocampal subfield volumes immediately after trauma and the development of PTSD symptoms 6 months later. We are aware of no studies that have examined how hippocampal subfields relate to PTSD symptom changes further from trauma exposure, that is, beyond the development phase of PTSD.

In the present study, we investigated whether Time 1 (assessed $M = 3.26$ years after returning from combat deployment) overall hippocampal and hippocampal subfield volumes predicted PTSD symptom changes approximately 2 years later in a relatively large group of 252 post-9/11 veterans with ($n = 159$) and without PTSD ($n = 93$) at their Time 1 assessment. Despite evidence of hippocampal plasticity (e.g., Admon et al., 2009), the volume of this structure has shown to be quite stable over time (e.g., Bigler et al., 1997; Wenger et al., 2014), and we did not expect substantial changes over a 2-year period. In contrast, PTSD symptoms tend to be more variable (e.g., Sripada et al., 2017), with some studies showing improvements over time (e.g., Lee et al., 2020) while others observing worsening symptoms (e.g., Mac Donald et al., 2021). We examined PTSD symptom changes by calculating the residual of Time 2 Clinical-Administered PTSD Scale (CAPS, for *Diagnostic and Statistical Manual of Mental Disorders, fourth Edition*, *DSM-IV*; Blake et al., 1995) symptoms after controlling Time 1, ensuring effects were not driven by regression to the mean. To segment the hippocampus, we used the validated automated algorithm in FreeSurfer 7.1 (Iglesias et al., 2015), which outputs volumes of 19 subfields in each hemisphere including the regions of interest (ROIs), the granule cell and molecular layer of the dentate gyrus (GC-ML-DG), CA2/3, and CA1. FreeSurfer outputs a combined CA2/3 rather than CA2 and CA3 because of difficulties isolating the CA2, which is particularly small. Further, this automated procedure subdivides subfields into head and body, allowing for more fine-grained distinctions than previous PTSD investigations. Based on PTSD treatment studies showing those with larger hippocampal volumes have better outcomes (Rubin et al., 2016; van Rooij et al., 2015) and the functional roles of the GC-ML-DG, CA1, and CA2/3 in PTSD, we hypothesized that smaller hippocampal subfield volumes in the GC-ML-DG, CA2/3, and CA1 (with no hypothesis on head, body, or laterality) would be associated with less PTSD symptom improvement over time. Secondarily, we examined whether other factors that may play a role in PTSD symptom changes accounted for the association between hippocampal subfield volume and PTSD symptom change, including combat exposure, treatment, days between assessments, and time since deployment. We further evaluated the association between hippocampal subfield volumes and PTSD symptom changes by examining their association with changes in PTSD symptom clusters. Finally, we also examined whether verbal learning and memory, cognitive processes that rely on the hippocampus (Aslaksen et al., 2018), were associated with hippocampal subfield volumes.

Method and Materials

Participants

Participants were 252 post-9/11 veterans recruited into the Translational Research Center for TBI and Stress Disorders (TRACTS), an ongoing longitudinal research project examining outcomes in post-9/11 veterans who returned for a Time 2 visit approximately 2 years later (mean days = 768.77, $SD = 353.5$). Data collection began in February of 2010 and new participants continue to be enrolled. This study was approved by the local VA Institutional Review Board (No. 2354) and was conducted in accordance with the Helsinki Declaration. All participants provided written and informed consent.

Participants were excluded from the study if they reported a history of moderate or severe traumatic brain injury (TBI), seizures or neurological illness (unrelated to head injuries), a current diagnosis of schizophrenia spectrum or other psychotic disorders (unrelated to PTSD), a current diagnosis of bipolar or related disorder (unrelated to PTSD), had an unstable psychological diagnosis that would interfere with accurate data collection (as determined by consensus of two doctorate-level psychologists), active suicidal or homicidal ideation, a cognitive disorder due to a general medical condition other than TBI, or if they were unable to undergo MRI due to ferromagnetic objects or pregnancy. Individuals were further excluded if they were missing psychiatric assessment data or if they failed the Medical Symptom Validity Test (Green, 2004), a sensitive and specific stand-alone effort measure (Clark et al., 2014).

Clinical and Cognitive Assessments

During each time point (Time 1 and Time 2), participants performed clinical and cognitive assessments as well as an magnetic resonance imaging (MRI) scan. PTSD diagnosis and severity were assessed with the CAPS for *DSM-IV* (Blake et al., 1995). The CAPS for *DSM-IV* was used because this study included participants who were enrolled prior to the release of CAPS-5. Military-related combat exposure was measured with the Deployment Risk and Resilience Inventory Section I–Combat Experiences (King et al., 2006) during the Time 1 session only (see Supplemental Materials). Combat exposure was unavailable for nine participants.

Treatment was defined as psychotropic medication management with at least one prescription refill and/or repeated psychotherapy sessions. Treatment was coded dichotomously, indicating the presence or absence of any treatment between Time 1 and Time 2, and was available for a subset of the sample ($n = 174$; see Supplemental Materials).

Verbal memory was measured using the California Verbal Learning Test–II (CVLT-II) standardized (z or t) scores on total learning trials, long-delay free recall, short-delay free recall, and recognition hits. This was part of the TRACTS battery administered at Time 1 and Time 2 and was examined as a task of convenience. CVLT-II was unavailable for six participants at Time 1 and three at Time 2.

Imaging Acquisition

Scanning was performed using a 3-Tesla Siemens whole-body TIM Trio MRI scanner or a Prisma^{fit} that was installed during

data collection. For the first 207 participants recruited into the study, two magnetization-prepared rapid gradient echo (MP-RAGE) T1-weighted structural scans were collected at Time 1: repetition time = 2,530 ms, time to echo = 3.32 ms, flip angle = 7°, field of view = 256, matrix = 256 × 256, voxel size = 1 mm^3. After a scanner upgrade, the remaining 45 participants had two MP-RAGE T1-weighted structural scans collected at Time 1 on a Siemens $Prisma^{fit}$ scanner with the same parameters, except the time to echo = 3.35 ms. All scans were acquired in the sagittal plane. At Time 2, 109 participants were scanned using the TIM Trio scanner and 104 were scanned using the Prisma. A scanner covariate was included in analyses to account for potential scanner differences (except when hippocampal volumes were averaged across time points). The two T1-weighted structural scans were averaged to create a high contrast-to-noise image. A second MP-RAGE was unavailable for nine individuals, and analyses for these individuals were completed with a single MP-RAGE T1-weighted structural scan.

Structural Image Processing and Hippocampal Subfield Volume Analysis

Structural neuroimaging processing including estimation of total intracranial volume (eTIV) was performed using the FreeSurfer image analysis suite, Version 7.1 (https://surfer.nmr.mgh.harvard.edu; Buckner et al., 2004; Dale et al., 1999; Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, & Tootell, 1999). Hippocampal subfield segmentation was performed with an automated pipeline released as part of FreeSurfer Version 7.1. This procedure yielded volumetric estimations of each subfield subdivided into head and body (when applicable) for a total of 19 subfields for each hemisphere. The details of the FreeSurfer automated segmentation are described in the original article (Iglesias et al., 2015). Briefly, the tool uses a probabilistic atlas built with ultra-high-resolution *ex vivo* MRI data (~0.1 mm isotropic) to produce an automated segmentation of the hippocampal substructures. This procedure also outputs whole hippocampus, hippocampal head, and hippocampal body estimates. Subfields include the parasubiculum, presubiculum-head, subiculum-head, CA1-head, CA2/3-head, CA4-head, GC-ML-DG-head, molecular layer of the hippocampus (molecular layer HP)-head, hippocampal amygdala transition area, presubiculum-body, subiculum-body, CA1-body, CA2/3-body, CA4-body, GC-ML-DG-body, molecular layer HP-body, fimbria, hippocampal tail, and hippocampal fissure. Figure 1 shows the hippocampal subfield segmentation from a sample subject.

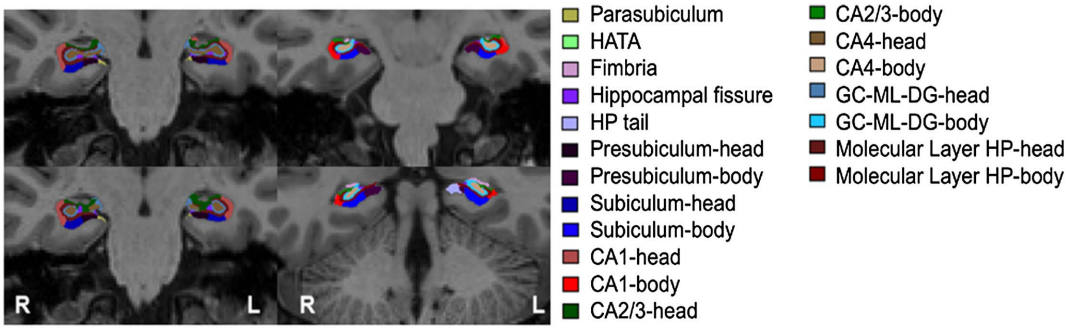
It is important to note that we segmented the hippocampus using automated procedures on 1 mm^3 T1-weighted images and recent concerns have been raised about the use of automated segmentations at this T1 resolution (Wisse et al., 2021). In particular, a significant limitation of the use of this procedure is that it depends on an atlas composed of *ex vivo* ultra-high-resolution images acquired on 7 T and then applies this information to delineate the inner structures of the hippocampus on 1 mm^3 T1-weighted images, a resolution in which visualization of these hippocampal structures has been questioned (Wisse et al., 2021). Further, these segmentations at the 1 mm^3 resolution have not been validated against manual segmentations as applied to the 1 mm^3 T1 images (Wisse et al., 2021). Thus, it may be warranted to use some caution when interpreting the results reported here. That being said, a recent test–retest reliability study of FreeSurfer's automated segmentation procedure with the same scanner and T1 resolution demonstrated high reliability within the structures reported here (Brown et al., 2020; Weis et al., 2021, see Sämann et al., 2022). Further, Brown et al. (2020) demonstrated good dice overlap cross-sectionally and excellent overlap longitudinally, which is a well-used statistical metric for verifying that some volumetric correspondence exists between the ground truth and the estimated labels. Finally, in the current data set, we report the reliability of the overall hippocampal and subfield volumes (see Supplemental Table S1), which was quite high for the majority of subfields, mean r = .96. As a robustness check for the key Time 1 volume analyses, we also performed analyses using Time 2 and Time 1/Time 2 average subfield volumes.

Statistical Analyses

R (https://www.R-project.org) and SPSS Version 26 (IBM Corp., Armonk, NY, United States) were used for statistical analyses. We began by examining the association between Time 1 hippocampal

Figure 1

Hippocampal Subfield Segmentation From a Sample Subject



Note. Coronal T1 MRI with the 19 FreeSurfer 7.1 subregions labeled. HATA = hippocampus–amygdala transition area; HP = hippocampus; CA = cornu ammonis; GC-ML-DG = granule cell and molecular layer of the dentate gyrus; MRI = magnetic resonance imaging. See the online article for the color version of this figure.

volume and Time 1 PTSD symptoms (regression model predicting PTSD symptoms). Given prior evidence for age and sex differences in hippocampal volume (Barnes et al., 2009; Nobis et al., 2019; Ruigrok et al., 2014) and that head size scales with brain structure (Mathalon et al., 1993; Synek & Reuben, 1976; Zatz & Jernigan, 1983), age, sex, and eTIV were included alongside scanner (TIM Trio or Prisma) as predictors. We additionally examined the following hypothesized subfield ROIs (both body and head): CA1, CA2/3, and GC-ML-DG. These were not corrected for multiple comparisons since these regions were hypothesized to be related to PTSD symptoms based on previous studies (e.g., Postel et al., 2021).

Next, we examined associations between Time 1 hippocampal volume and changes in PTSD symptoms (regressing Time 1 CAPS scores out of the Time 2 CAPS scores), controlling for age, sex, scanner, and eTIV. We performed these analyses across the entire sample as well as separately in those with and without a PTSD diagnosis. We followed this up with head/body ROI analyses of our three hypothesized subfields: CA1, CA2/3, and DG. We additionally performed exploratory analyses for the remaining 13 hippocampal subfields, controlling for multiple comparisons using a false-discovery rate (FDR) correction of .05 (Benjamini & Yekutieli, 2001, significant effects were those with q-values < 0.05). Considering that subfield volumes are highly reliable (see Brown et al., 2020, and results below) and should not appreciably change over a 2-year period during this many years posttrauma, as a robustness check for significant subfield effects we repeated the analyses using Time 2 volume and the average of Time 1 and Time 2 volumes in a slightly reduced sample ($n = 213$; 39 individuals did not have Time 2 MRI scans available). We next examined whether any significant subfield effects observed differed between left and right hemisphere volumes. We additionally examined if the association between PTSD symptom changes and hippocampal subfield volume was specific to any PTSD symptom clusters (reexperiencing, avoidance/numbing, or hyperarousal) by running a hierarchical linear regression where covariates (age, sex, scanner, and eTIV) were included in Step 1 and the three PTSD symptom cluster residuals were included in Step 2 predicting ROI hippocampal subfield volumes and exploratory subfields after FDR correction (see Supplemental Table S3). Finally, to understand if hippocampal or subfield ROI volumes were associated with learning and memory performance, in exploratory analyses we examined the CVLT-II t- and z-scores for total learning trials, long-delay free recall, short-delay free recall, and recognition hits at both Time 1 as well as changes in performance.

To rule out alternative explanations relevant to PTSD, we investigated the hierarchical models of the whole hippocampus and hippocampal subfields predicting the CAPS residuals by running separate models including either trauma exposure, treatment history, days between assessments, or time since deployment along with the covariates of age, sex, scanner, and eTIV (see Supplemental Materials).

Sample Size Justification

The present study is part of a large ongoing longitudinal project (TRACTS; McGlinchey et al., 2017), which provided a sample size of 252 participants, slightly larger than previous longitudinal hippocampal PTSD studies ($n = 215$; Weis et al., 2021). With our sample size of 252, $\alpha = .05$, and power $1 - \beta = 0.80$, we estimate having the sensitivity to detect a correlation of $r = .18$ between changes in PTSD symptoms and hippocampal subfield volume. Given that past studies have observed significant associations between hippocampal volume and PTSD symptom changes in those with PTSD diagnoses (e.g., CA1 volume and intrusion symptoms, $\beta = -.27$; CA2/3 volume and hyperarousal symptoms, $\beta = -.26$; Postel et al., 2021), we estimated that we would have adequate sensitivity to detect similar relationships.

Transparency and Openness

We report how we determined our sample size, all data exclusions, manipulations, and measures in the study. There was no prior dissemination of this data. The study design and analysis plan were not preregistered. Raw data files are available following standard data sharing protocols at the VA Boston Institutional Review Board. Computer syntax is available through SPSS and R upon request. Please contact Dr. Joseph DeGutis at degutis@wjh.harvard.edu. The VA Boston Healthcare System Institutional Review Board approved this study (No. 2354, Translational Research Center for Traumatic Brain Injury and Stress Disorders: Human Characterization Core B), written consent was obtained from all participants, and research was conducted in accordance with the Declaration of Helsinki.

Results

Participants

Table 1 lists the Time 1 demographic and clinical characteristics of the sample, which was a relatively young ($M = 32.75$ years), predominantly male (90.10%) veteran cohort. The average Time 1 CAPS-IV score was 48.34, and the average CAPS difference score was −5.00, suggesting that PTSD symptom severity generally decreased from Time 1 to Time 2. Additionally, the average Time 1 Depression Anxiety Stress Scale depression score was 8.75, and the average change in depression score was −0.33. Of note, out of 252 participants, 90 did not have PTSD at either time point, 106 veterans had PTSD at both time points, 40 veterans recovered from PTSD at Time 2, and 16 veterans developed PTSD at Time 2.

Smaller Whole Hippocampal Volume Is Associated With Greater PTSD Symptoms

We first sought to replicate findings in the literature that *greater* current PTSD symptom severity is associated with *smaller* whole hippocampal volume. We examined the association between Time 1 PTSD symptom severity and whole hippocampal volume and found a significant negative association (after controlling for age, sex, scanner, and eTIV), such that those with higher PTSD symptom severity had smaller hippocampal volumes ($\beta = -0.11$, $p = .039$). However, this finding failed to reach significance when covariates were excluded ($r = -0.04$, $p = .564$; see Supplemental Figure S1). There were also no significant differences between those with and without PTSD diagnosis (PTSD+ $M = 3757.84$, $SD = 331.62$; PTSD− $M = 3748.48$, $SD = 359.76$, $t = 0.21$, $p = .833$). When examining Time 1

Table 1
Demographic and Clinical Characteristics

Variable	Total sample (N = 252)
Age, *M* (*SD*)	32.75 (8.49)
Sex	
Males, *n* (%)	227 (90)
Females, *n* (%)	25 (10)
Scanner (trio), *n* (%)	207 (82)
eTIV, *M* (*SD*)	1623921.63 (172067.38)
Total bilateral whole hippocampus volume, *M* mm^3 (*SD*)	3752.42 (347.55)
Total bilateral whole hippocampal head volume, *M* mm^3 (*SD*)	1851.85 (197.49)
Total bilateral whole hippocampal body volume, *M* mm^3 (*SD*)	1281.45 (121.13)
Days between Time 1 and Time 2, *M* (*SD*)	768.77 (353.54)
Months since deployment, *M* (*SD*)[a]	39.40 (36.10)
Military mTBI (yes), *n* (%)	110 (44)
Lifetime mTBI (yes), *n* (%)	163 (65)
PTSD diagnosis Time 1 (yes), *n* (%)	146 (58)
PTSD diagnosis Time 2 (yes), *n* (%)	130 (48)
CAPS-IV Time 1, *M* (*SD*)	48.34 (28.19)
CAPS-IV Time 2, *M* (*SD*)	43.35 (28.74)
CAPS difference score, *M* (*SD*)	−5.00 (20.55)
CAPS reexperiencing difference score, *M* (*SD*)	−1.70 (7.84)
CAPS avoidance/numbing difference score, *M* (*SD*)	−2.21 (9.89)
CAPS hyperarousal difference score, *M* (*SD*)	−1.09 (7.97)
DASS depression Time 1, *M* (*SD*)	8.37 (9.56)
DASS depression difference score, *M* (*SD*)	−0.33 (7.99)
DASS anxiety Time 1, *M* (*SD*)	6.24 (7.54)
DASS anxiety difference score, *M* (*SD*)	0.19 (7.05)
Combat exposure (DRRI-combat), *M* (*SD*)[b]	16.54 (11.86)
Treatment (yes), *n* (%)[c]	57 (77)

Note. eTIV = estimated total intracranial volume; mTBI = mild traumatic brain injury; PTSD = posttraumatic stress disorder; CAPS = Clinician-Administered PTSD Scale; DASS = Depression Anxiety Stress Scale; DRRI = Deployment Risk and Resiliency Inventory.
[a] Data were unavailable for 14 participants. [b] Data were unavailable for nine participants. [c] Treatment data were available for 174 participants and included both psychotherapy and pharmacologic treatment.

CAPS associations with the hippocampal subfield ROIs, none were significant ($p \geq .452$).

Smaller Hippocampal Subfield Volumes Are Associated With Greater PTSD Symptom Improvement Over Time

We then examined the association between whole hippocampal volume and PTSD symptom change residuals.[1] Smaller hippocampal volume was weakly and nonsignificantly associated with greater PTSD symptom improvement over time ($\beta = 0.06$, $p = .209$, controlling for age, sex, scanner, and eTIV).

We next examined the associations between hippocampal subfields and PTSD symptom change, focusing on hypothesized CA1, CA2/3, and dentate gyrus (GC-ML-DG) ROIs. After controlling for covariates, we found that *smaller* Time 1 bilateral CA1-body volume ($\beta = 0.18$, $p = .009$; see Table 2) and CA2/3-body volume ($\beta = 0.14$, $p = .039$; see Table 2) were significantly associated with *greater* PTSD symptom improvement over time. As can be seen in Figure 2, these relationships were also statistically significant when excluding covariates. The CA1-body and CA2/3-body associations were similar for the right- and left-sided volumes (see Supplemental Materials). For the other hypothesized ROIs, the CA2/3-head was only numerically associated with improved PTSD symptoms ($\beta = 0.10$, $p = .061$), and CA1-head, GC-ML-DG-head, and GC-ML-DG-body showed nonsignificant associations ($p > .240$). Exploratory analyses of the remaining 13 hippocampal subregions did not reveal any significant PTSD change associations after FDR correction (see Supplemental Table S2).

Because the reliabilities of hippocampal subfield volumes tend to be less than the whole hippocampus (Brown et al., 2020), to ensure the robustness of these findings, we repeated these analyses using Time 2 subfield volumes as well as the average of subfields at Time 1 and Time 2. Results were very similar for CA1-body volume averaged across both time points ($\beta = 0.24$, $p < .001$) and Time 2 volume ($\beta = 0.23$, $p < .001$), as well as CA2/3-body (average: $\beta = 0.18$, $p = .008$; Time 2: $\beta = 0.17$, $p = .016$).

We next sought to determine whether the CA1-body and CA2/3-body associations were similar in those with and without a PTSD diagnosis at Time 1. For the CA1-body, there were similar associations with CAPS change in those with a PTSD diagnosis ($\beta = 0.14$, $p = .086$) and those without ($\beta = 0.18$, $p = .061$); see Figure 2A. For the CA2/3-body, there was a significant association with CAPS residuals in those *without* a PTSD diagnosis ($\beta = 0.23$, $p = .019$), but not in those with PTSD ($\beta = 0.05$, $p = .525$); see Figure 2B.

Associations Between Hippocampal Subfields and Changes in PTSD Symptoms Clusters

We next examined whether the significant associations between the hippocampal CA1-body and CA2/3-body volumes and PTSD symptom changes were specific to reexperiencing, avoidance/numbing, or hyperarousal clusters. As can be seen in Table 3, we conducted a hierarchical linear regression predicting subfield volume, where covariates (age, sex, scanner, and eTIV) were included in Step 1 and changes in the three PTSD symptom clusters were included in Step 2 (see Supplemental Table S3 for all subfield regions). Avoidance/numbing changes predicted unique variance in CA1-body volume ($\beta = 0.29$, $p < .001$), whereas reexperiencing and hyperarousal changes did not ($\beta = 0.02$, $p = .737$; $\beta = -.14$, $p = .064$, respectively).[2] Avoidance/numbing symptom changes similarly predicted the average CA1-body volume across time points ($\beta = 0.30$, $p < .001$) and at Time 2 ($\beta = 0.33$, $p < .001$). Results in the CA2/3-body volume showed a similar overall pattern, with avoidance/numbing changes numerically predicting unique variance in bilateral CA2/3-body volume at Time 1 ($\beta = 0.15$, $p = .056$), but not reexperiencing ($\beta = 0.11$, $p = .137$) or hyperarousal changes ($\beta = -0.12$, $p = .142$); see Table 3. Avoidance/numbing symptom changes similarly predicted unique variance in CA2/3-body volume at Time 2 ($\beta = 0.19$, $p = .031$) and showed a similar

[1] Time 1 and Time 2 CAPS were significantly correlated ($r = 0.74$, $p < .001$). Further, Time 1 CAPS was significantly associated with Time 1 minus Time 2 CAPS ($r = 0.34$, $p < .001$), suggesting a moderate regression-to-the-mean effect.
[2] Avoidance/numbing change residuals were moderately correlated with reexperiencing ($r = 0.51$, $p < .001$) and hyperarousal change residuals ($r = 0.57$, $p < .001$).

Table 2
Predicting CAPS Residuals From Hippocampal Subfield Volumes

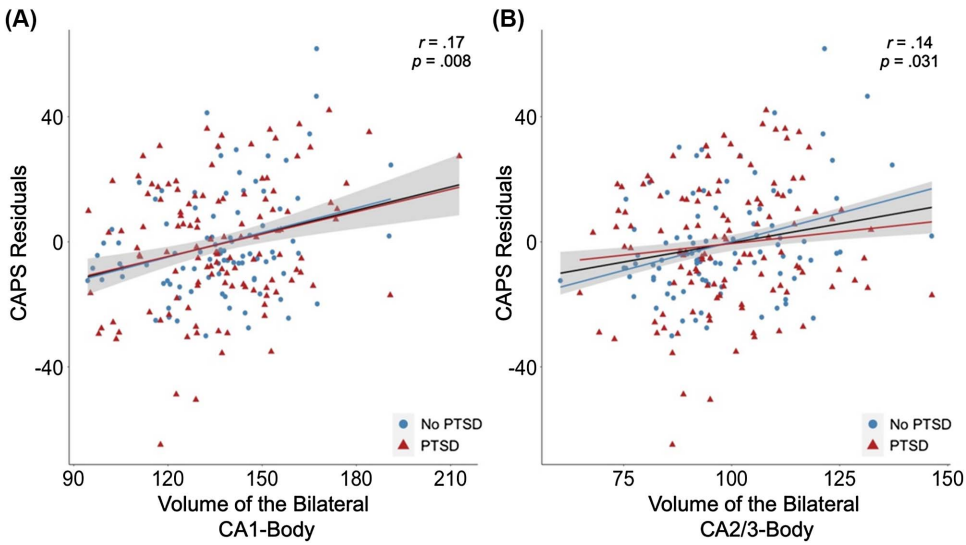
Variable	Model 1: Bilateral CA1-body at Time 1 Predicting CAPS residuals			Model 2: Bilateral CA2/3-body at Time 1 Predicting CAPS residuals		
	B	β	*p*	*B*	β	*p*
Step 1						
Age	0.12	0.05	.434	0.12	0.05	.418
Sex	3.04	0.05	.434	3.04	0.05	.434
Scanner	−7.75	−0.06	.547	−7.75	−0.06	.547
eTIV	0.00	0.00	.530	0.00	0.00	.530
Step 2						
Age	0.11	0.05	.448	0.09	0.04	.534
Sex	2.80	0.04	.760	2.83	0.04	.573
Scanner	−2.23	−0.05	.561	−2.41	−0.05	.479
eTIV	0.00	0.00	.953	0.00	0.02	.851
Bilateral CA1-body	0.16	0.18	.009	—	—	—
Bilateral CA2/3-body	—	—	—	0.17	0.14	.039
R^2 (adjusted R^2)	Step 1		0.01 (−0.01)	Step 1		0.01 (−0.01)
	Step 2		0.03 (0.01)	Step 2		0.02 (0.00)

Note. Subfields were averaged across hemispheres. *B* = unstandardized betas; β = standardized betas; CAPS = Clinician-Administered PTSD Scale; PTSD = posttraumatic stress disorder; CA = cornu ammonis; eTIV = estimated total intracranial volume; FDR = false-discovery rate.

trend for the average CA2/3-body volume across time points (β = 0.15, $p = .095$).

It is notable that both CA1-body and CA2/3-body showed an opposite relationship between volume and avoidance/numbing versus hyperarousal subscale changes, as did CA4-head and molecular layer HP-head in exploratory analyses (see Supplemental Table S3). Indeed, when examining the whole hippocampus at Time 1, *smaller* volume was significantly associated with *improved* avoidance/numbing symptoms over time (β = 0.24, $p < .001$) and *worsened* hyperarousal symptoms over time (β = −0.13, $p = .044$).

Figure 2
Association of CAPS Residuals With Time 1 Volume of (A) CA1-Body and (B) CA2/3-Body



Note. More negative CAPS residuals indicate a greater reduction in PTSD symptoms. Gray shading indicates the 95% confidence interval of the regression lines. Blue circles/regression lines indicate no PTSD diagnosis at Time 1, and red triangles/regression lines indicate PTSD diagnosis at Time 1. CA = cornu ammonis; CAPS = Clinician-Administered PTSD Scale; PTSD = posttraumatic stress disorder. See the online article for the color version of this figure.

Table 3
Predicting Subfield Volumes From CAPS Symptom Cluster Residuals

Variable	Model 1: Predicting bilateral CA1-body at Time 1			Model 2: Predicting bilateral CA2/3-body at Time 1		
	B	β	*p*	*B*	β	*p*
Step 1						
Age	0.03	0.01	.848	0.14	0.08	.215
Sex	1.50	0.02	.772	1.25	0.02	.748
Scanner	−2.85	−0.05	.394	−2.00	−0.05	.428
eTIV	0.00	0.26	<.001	0.00	0.26	<.001
Step 2						
Age	0.02	0.01	.913	0.13	0.07	.254
Sex	−0.14	0.00	.978	−0.13	0.00	.974
Scanner	−3.97	−0.07	.229	−2.44	−0.06	.333
eTIV	0.00	0.24	.001	0.00	0.24	.002
Reexperiencing	0.07	0.02	.737	0.25	0.11	.137
Avoidance/numbing	0.63	0.29	<.001	0.25	0.15	.056
Hyperarousal	−0.40	−0.14	.064	−0.24	−0.12	.142
R^2 (adjusted R^2)	Step 1		0.06 (0.05)	Step 1		0.06 (0.04)
	Step 2		0.12 (0.10)	Step 2		0.09 (0.07)

Note. Subfields were averaged across hemispheres. All three PTSD symptom cluster residuals (reexperiencing, avoidance/numbing, and hyperarousal) were included in the same model, calculated by residualizing Time 2 from Time 1 values. *B* = unstandardized betas; β = standardized betas; CAPS = Clinician-Administered PTSD Scale; PTSD = posttraumatic stress disorder; CA = cornu ammonis; eTIV = estimated total intracranial volume.

Analysis of the Association Between Verbal Memory and Hippocampal Subfield Volumes

We next performed exploratory analyses to determine if hippocampal subfield volumes were associated with learning and memory performance. We examined the CVLT-II (administered at Time 1 and Time 2) total learning trials, long-delay free recall, short-delay free recall, and recognition hits. We found no significant associations between Time 1 CA1-body volume or CA2/3-body volume with Time 1 CVLT-II performance or changes in CVLT-II performance ($p > .056$; see Supplemental Materials).[3]

Ruling Out Alternative Explanations: Combat Exposure, Treatment, Time Between Assessments, Time Since Deployment, and Repeat Assessment Sampling Bias

The association between smaller CA1-body and CA2/3-body volumes and improved PTSD symptoms over time could potentially be driven by several factors that we did not include in our models above, which we sought to rule out. The associations between Time 1 CA1-body or CA2/3-body and CAPS residuals did not change when either combat exposure, treatment history, days between assessments, or time since deployment were included in the models (see Supplemental Materials). Additionally, because there could be differences between participants who returned for their Time 2 assessment (64%) versus those who did not, we compared Time 1 demographic/clinical characteristics between the current sample and those from the original TRACTS cohort who did not return after >5 years ($n = 140$; see Supplemental Table S4). The only significant difference was time since deployment at Time 1, where those who did not return had a shorter time since deployment ($M = 14.62$ months) than the present sample ($M = 39.40$, $t = 7.97$, $p < .001$). This was expected because nonreturning participants had to have at least 5 years pass from Time 1, biasing the sample to have earlier Time 1 assessments.

Discussion

This study investigated the association between whole hippocampus/subfield volumes and PTSD symptom severity changes over an approximately two-year period. First, replicateing previous findings, our results showed that greater Time 1 PTSD symptom severity (assessed $M = 3.28$ years after returning from last deployment) was associated with smaller whole hippocampal volume. However, when we examined this association with PTSD symptom changes (Time 2 residuals after controlling for Time 1), we found that PTSD symptom improvements over time were associated with *smaller* hippocampal subfield volumes, specifically in the CA1-body and CA2/3-body subfields. This relationship could not be explained by regression to the mean, trauma exposure, treatment history, days between assessments, or time since deployment. Further, there was a unique association between smaller volume in the CA1-body and CA2/3-body and improvements in avoidance/numbing symptoms. These results suggest that, paradoxically, *smaller* hippocampal CA1-body and CA2/3-body volumes may be associated with a greater likelihood of PTSD symptoms improving over time, particularly avoidance and numbing symptoms.

Our results demonstrate that Time 1 PTSD symptom severity was associated with smaller Time 1 whole hippocampal volume after accounting for covariates (e.g., head size, age, sex). This finding is consistent with a large body of work, including several meta-analyses, that point to smaller overall hippocampal volume being

[3] Given that the scaled verbal memory measures were a mixture of *t* and *z* scores, we reran these analyses using the raw scores. The pattern of results did not change for the associations between Time 1 or changes in verbal memory and the volumes of the left or right CA1-body or molecular layer HP-body at Time 1 ($p > .200$).

associated with greater PTSD symptoms (Karl et al., 2006; Kitayama et al., 2005; Kühn & Gallinat, 2013; Logue et al., 2018; O'Doherty et al., 2015; Smith, 2005; Woon et al., 2010). Interestingly, when we examined whether the greater volume of the whole hippocampus was associated with PTSD symptom improvements over time, we found no significant relationship and this was numerically in the opposite direction ($\beta = 0.06$, $p = .209$). When breaking up the results by symptom clusters, we notably found that *smaller* hippocampal volume was related to significantly *improved* avoidance/numbing symptoms but *worsened* hyperarousal symptoms. This contrasts with prior treatment studies, which have shown that larger overall hippocampal volume is associated with better treatment response (Suarez-Jimenez et al., 2020; Rubin et al., 2016; Zilcha-Mano et al., 2023). However, these studies had smaller sample sizes ($n \leq 76$), were investigating much shorter Time 1–Time 2 intervals (6–12 weeks), and Time 1 was closer to participants' trauma (e.g., within 2 years, Butler et al., 2018).

The current findings may help to explain heterogeneous findings in the literature, with some studies showing associations between hippocampal volume and PTSD diagnosis or symptom severity (e.g., Kühn & Gallinat, 2013; Logue et al., 2018) and others showing little-to-no associations (e.g., Bonne et al., 2001; Golier et al., 2005). Our results suggest that hippocampal size could be associated with mechanistically different PTSD symptom changes over time in those with more chronic PTSD and that there may be dissociations between avoidance/numbing and hyperarousal symptoms. Whereas previous studies have observed that those with a larger hippocampus may be less likely to develop PTSD (e.g., Gilbertson et al., 2002; Kremen et al., 2012; Pitman et al., 2006), our results suggest that those with smaller subfields of the hippocampus may be less likely to have worsening levels of PTSD once symptoms are already chronic, particularly avoidance/numbing symptoms. Further, the current findings provide neurobiological evidence for the behavioral distinction between the risk factors for the development versus maintenance of PTSD (Brewin, 2005; Johnson & Thompson, 2008; Meyer et al., 2019; Schnurr et al., 2004) and suggest that hippocampal volume may serve mechanistically different roles in these processes. Together, these results provide a more complicated and nuanced model of the role of the hippocampus in PTSD.

With regard to the hippocampal subfield analyses, contrary to our hypothesis, we found that PTSD symptom improvements were associated with smaller CA1-body and CA2/3-body volumes. Although previous work has reported smaller CA1 (Chen et al., 2018; Postel et al., 2021) and CA2/3 volumes (Averill et al., 2017; Postel et al., 2021; Wang et al., 2010) in those with *increased* PTSD symptoms, these studies were cross sectional. Here, we investigated hippocampal subfields in relation to changes in PTSD symptom severity over time. In experimental models of PTSD, CA1 and CA3 are implicated in fear learning (e.g., Cravens et al., 2006), and CA1 has been implicated in fear-related memory retrieval (Sans-Dublanc et al., 2020; Zamorano et al., 2018). Additionally, Zhou et al. (2017) demonstrated that neuronal connections in the CA1 are involved in fear generalization. Thus, one possibility is that larger CA1-body and CA2/3-body volumes may be associated with increased connections that then may lead to overgeneralization of trauma memories, which could contribute to the maintenance of PTSD symptoms over time (though see Levy-Gigi et al., 2015; Postel et al., 2021). Moreover, as overgeneralization of memory is associated with avoidance (Hauer et al., 2006; Norbury et al., 2018; Schönfeld et al., 2007; van Meurs et al., 2014; Williams, 2006), this could also explain the specific relationship observed between larger CA1-body and CA2/3-body and increased avoidance/numbing symptoms over time.

Together, our findings of smaller CA1-body and CA2/3-body being related to reduced PTSD symptoms over time are consistent with previous work showing that smaller hippocampal volumes in the anterior hippocampus (CA1-body and CA2/3-body are more represented anteriorly) may lead to better treatment outcomes (Suarez-Jimenez et al., 2020; Rubin et al., 2016; Zilcha-Mano et al., 2023, but see van Rooij et al., 2015), potentially suggesting that larger anterior hippocampal subfield volumes may have negative consequences for PTSD outcomes. Interestingly, we did not find any relationship between PTSD symptom changes and previously reported PTSD-associated subfields including the DG (Hayes et al., 2017; Wang et al., 2010), suggesting that these subfields may not play as large of a role in the maintenance of PTSD symptoms over time.

Disruptions in verbal learning and memory are a core feature of PTSD (Brewin, 2011; Johnsen & Asbjørnsen, 2008; K. M. Shin et al., 2015; Verfaellie & Vasterling, 2009), which have been associated with disruptions in hippocampal activation in PTSD (Bremner et al., 2003; Carrión et al., 2010; Hayes et al., 2011; Werner et al., 2009). Thus, it is possible that alterations in the CA1-body and CA2/3-body may be particularly important in the maintenance of PTSD symptoms and may be involved in disruptions to verbal memory in PTSD. However, when we examined associations between Time 1 verbal memory/changes in verbal memory with the volumes of the CA1-body and CA2/3-body directly, we did not find significant associations and were unable to support this hypothesis. One explanation for this discrepancy is that the verbal memory measures used in the present study were not sensitive enough to PTSD-related hippocampal disruptions. It will be important for future work to continue to investigate the association between hippocampal subfields and memory performance with more sensitive behavioral measures.

This study should be considered within the context of its limitations. This is a predominantly male, veteran cohort, and it is unclear whether these findings generalize to other populations. Additionally, we segmented the hippocampus using automated procedures from FreeSurfer, Version 7.1 on 1 mm^3 T1-weighted images, and recent concerns have been raised about the use of automated segmentations on this T1 resolution (Wisse et al., 2021). However, these concerns may be offset by a recent test–retest reliability study of FreeSurfer's automated segmentation procedure conducted on the same scanner as the present study, which showed that both the CA1-body and CA2/3-body exhibited high reliability (see Supplemental Table S1 as well as Brown et al., 2020; Weis et al., 2021). Nonetheless, given the concerns raised by Wisse et al. (2021), these results should be interpreted with caution until future work can replicate these findings with subfields delineated with higher resolution images and manual segmentations. Further, although every effort was made to bring individuals back for Time 2 after approximately 2 years from their Time 1 visit, there was some variation in time between assessments, which may have added noise to the data. However, the results did not change when controlling for days between assessments. An additional consideration is that the first time point was years posttrauma, reflecting more chronic PTSD. Thus, it is not possible to determine if

hippocampal volume is a risk factor for PTSD development or whether the association between hippocampal volume and Time 1 PTSD was influenced by other factors after the initial trauma exposure. Another limitation is that this study used the CAPS for *DSM-IV*. Since the participation in this study, the CAPS-5 has been released, which includes a slightly different categorization of symptom clusters. It will be important for future work to reexamine these associations with the total and symptom cluster scores of the CAPS-5. Finally, the current results were collected at two time points, and additional time points would have allowed a better examination of the trajectory of PTSD symptoms.

In summary, we observed the novel finding that smaller subfield volumes of the CA1-body and CA2/3-body at Time 1 were associated with greater PTSD symptom improvement over time, particularly improvements in avoidance/numbing symptoms. This supports a more complex and nuanced model of hippocampal volume in PTSD, where during the posttrauma years bigger may not always mean better, and suggests that the CA1-body and CA2/3-body are important factors in the maintenance of PTSD symptoms. Along with other behavioral (e.g., inhibitory control, DeGutis et al., 2023) and clinical measures (e.g., alcohol use, Lee et al., 2020), these subfield measures could be used to construct predictive models of who are most and least likely to improve their PTSD and lead to more targeted and individualized treatment approaches.

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