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Stability of hippocampal subfield volumes after trauma and relationship to development of PTSD symptoms

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ABSTRACT

Background: The hippocampus plays a central role in post-traumatic stress disorder (PTSD) pathogenesis, and the majority of neuroimaging research on PTSD has studied the hippocampus in its entirety. Although extensive literature demonstrates changes in hippocampal volume are associated with PTSD, fewer studies have probed the relationship between symptoms and the hippocampus' functionally and structurally distinct subfields. We utilized data from a longitudinal study examining post-trauma outcomes to determine whether hippocampal subfield volumes change post-trauma and whether specific subfields are significantly associated with, or prospectively related to, PTSD symptom severity. As a secondary aim, we leveraged our unique study design sample to also investigate reliability of hippocampal subfield volumes using both cross-sectional and longitudinal pipelines available in *FreeSurfer v6.0*.

Methods: Two-hundred and fifteen traumatically injured individuals were recruited from an urban Emergency Department. Two-weeks post-injury, participants underwent two consecutive days of neuroimaging (time 1: T1, and time 2: T2) with magnetic resonance imaging (MRI) and completed self-report assessments. Six-months later (time 3: T3), participants underwent an additional scan and were administered a structured interview assessing PTSD symptoms. First, we calculated reliability of hippocampal measurements at T1 and T2 (automatically segmented with *FreeSurfer* v6.0). We then examined the prospective (T1 subfields) and cross-sectional (T3 subfields) relationship between volumes and PTSD. Finally, we tested whether change in subfield volumes between T1 and T3 explained PTSD symptom variability.

Results: After controlling for sex, age, and total brain volume, none of the subfield volumes (T1) were prospectively related to T3 PTSD symptoms nor were subfield volumes (T3) associated with current PTSD symptoms (T3). Tl – T2 reliability of all hippocampal subfields ranged from good to excellent (intraclass correlation coefficient (ICC) values > 0.83), with poorer reliability in the hippocampal fissure.

Conclusion: Our study was a novel examination of the prospective relationship between hippocampal subfield volumes in relation to PTSD in a large trauma-exposed urban sample. There was no significant relationship between subfield volumes and PTSD symptoms, however, we confirmed *FreeSurfer v6.0* hippocampal subfield segmentation is reliable when applied to a traumatically-injured sample, using both cross-sectional and longitudinal analysis pipelines. Although hippocampal subfield volumes may be an important marker of individual variability in PTSD, findings are likely conditional on the timing of the measurements (e.g. acute or chronic post-trauma periods) and analysis strategy (e.g. cross-sectional or prospective).

1. Introduction

The hippocampus is a brain structure of the medial temporal lobe known primarily for its role in supporting learning and memory functions (Jin and Maren, 2015; Joshi et al., 2020; Knierim, 2015; Maren et al., 2013; Wixted and Squire, 2011). Work with rodents and human case studies with selective hippocampal damage (e.g., patient H.M.; Squire, 2009) has thoroughly documented the structure and function of the hippocampus (Bartsch and Wulff, 2015; Coburn, 2018; Knierim, 2015; Lupien and Lepage, 2001; Phillips and LeDoux, 2021; Preston-Ferrer and Burgalossi, 2018; Tatu and Vuillier, 2014; Witter et al., 2017). Comprised of several subfields with specialized cytoarchitecture, connectivity, and function including Cornu Ammonis (CA) 1–4, dentate gyrus (DG), presubiculum, subiculum, and parasubiculum, the hippocampus is integral for a myriad of mnemonic functions, such as the

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formation of fear memory traces (e.g., Coburn, 2018; El-Falougy and Benuska, 2006; Haukvik et al., 2018; Radonjic et al., 2014; Witter et al., 2017).

A substantial body of literature indicates the hippocampus is particularly vulnerable to stress from exposure to stress hormones produced by activity of the hypothalamic-pituitary-adrenal (HPA) axis (Bartsch and Wulff, 2015; Kim et al., 2015; Lupien and Lepage, 2001; McEwen et al., 2016; Miller and O'Callaghan, 2005; Ortiz and Conrad, 2018). Morphological, structural, and functional changes of the hippocampus have been reported in an array of psychological disorders, including posttraumatic stress disorder (PTSD; Besnard and Sahay, 2016; Coburn, 2018; Hayes et al., 2017; Lazarov et al., 2017; Logue et al., 2018; Malivoire et al., 2018; Rangaprakash et al., 2017; Tural et al., 2018; van Rooij et al., 2018). PTSD, which may develop as a consequence of experiencing a trauma, is a debilitating psychiatric disorder (Fenster et al., 2018; Mahan and Ressler, 2012). Symptoms include re-experiencing the traumatic event (e.g., flashbacks), avoidance of stimuli associated with the event, negative affect and cognition, and heightened arousal (American Psychiatric Association, 2013). Differences in hippocampus volume, as well as function, are theorized to underly memory issues frequently present in individuals with PTSD (Joshi et al., 2020; Liberzon and Sripada, 2007; McEwen et al., 2016; Shin, 2006).

A number of scholars have suggested hippocampal volume is a biomarker of risk for PTSD development (i.e., vulnerability factor; Gilbertson et al., 2002; Gurvits et al., 2006; Kremen et al., 2012; Wang et al., 2010; Xie et al., 2018) *and/or* asserted that changes in volume track with PTSD symptoms (i.e., are caused by the resulting psychological sequela; Apfel et al., 2011; Gurvits et al., 1996; Woon and Hedges, 2008). Although more sparse, additional work has demonstrated null findings, suggesting smaller hippocampus volume is neither a risk factor nor a consequence of PTSD (e.g., Bonne et al., 2001). Notably, the majority of this work has referenced the whole volume (Bonne et al., 2001; Chen et al., 2018).

Closer examination of hippocampal subfields may afford greater precision to the utility of the region as a biomarker of PTSD. In addition, each subfield may play a differential role in symptom development. Impaired extinction of fear memories and over-consolidation of fear, are two hallmarks of PTSD development which may result from specific subfield functional and/or structural abnormalities (Mahan and Ressler, 2012). Select studies, with both adolescents and adults, have segmented the hippocampus into its subfields and demonstrated that PTSD symptom severity is associated with smaller dentate gyrus (Hayes et al., 2017; Postel et al., 2019; Wang et al., 2010), CA1 (Chen et al., 2018), hippocampus-amygdala transition area (Ahmed-Leitao et al., 2016; Averill et al., 2017); , and parasubiculum (Ahmed-Leitao et al., 2016).

Specific neurocircuitry within the hippocampus, as described in animal models, would suggest particular behavioral effects (i.e., aberrant memory formation, consolidation, retrieval) emerge when different hippocampal subfields are perturbed (Phillips and LeDoux, 2021; Preston-Ferrer and Burgalossi, 2018). For example, decreased volume in the dentate gyrus, a region proposed to underlie pattern separation processes, may contribute to overgeneralization of fear, a common theoretical model of PTSD (Hayes et al., 2017). Together the dentate gyrus and CA3 also work together to encode and retrieve spatial information, while the CA1 is essential for a myriad of mnemonic tasks, including autobiographical memory (Bartsch et al., 2011). The parasubiculium is also linked to processing spatial information (Dalton and Maguire, 2017). Although future work is required, these findings collectively suggest PTSD is linked with decreased volume of hippocampal subfields responsible for holistic representations of scenes and offer a potential mechanism by which trauma impacts hippocampal activity and memory (Miller and Wiener, 2014).

The current evidence suggests that differences in hippocampal subfield volumes may reflect a predisposition to PTSD as well as correspond to post-trauma symptom trajectories. However, the current literature is lacking evidence as to whether hippocampal subfield volumes measured *acutely* post-trauma are prospectively related to PTSD symptoms. If subfield volumes are to be a useful biomarker for post-trauma individual risk and resilience, the measurement of the volumes must be valid – capture the individual differences associated with PTSD – and be reliably measured (Dhama et al., 2019; Lehrner and Yehuda, 2014; Mayeux, 2004). Therefore, reliable measurement of hippocampal structure and subfields is important for accurate monitoring of morphological and volumetric changes that accompany PTSD (Bartsch and Wulff, 2015; Burke and Barnes, 2010; Fröhner et al., 2019).

Although measurement of the whole hippocampus has proven reliable (Ahmed-Leitao et al., 2016; Brown et al., 2020; Hsu et al., 2002; Mulder et al., 2014; Schmidt et al., 2018), until recently, the small size of the subfields made assessing volumes challenging (Brown et al., 2020). Manual segmentation of the hippocampus and its subfields used to be the gold standard for segmentation despite the highly subjective process that depends heavily on the expertise of the evaluator (Dill et al., 2015; Yushkevich et al., 2015a,b). However, enhanced resolution of structural magnetic resonance imaging (MRI) technology and new segmentation programs have allowed for more quantitative approaches using atlases and probabilistic features of structural MRI data, making automated pipelines for hippocampal subfield segmentation a commonly used analytic tool (Dill et al., 2015). Although higher resolution images typically offer the most accurate segmentation (Wisse et al., 2016; Yushkevich et al., 2009), previous work has concluded automatic segmentation of hippocampal subfields in lower resolution images yields accurate measurements compared to manual edits (Yushkevich et al., 2015a,b).

FreeSurfer is perhaps the most widely used tool for automated tissue parcellation and cortical and subcortical segmentation (Fischl et al., 2002). Hippocampal subfield reliability processed through *FreeSurfer* has been evaluated across scanners (Marizzoni et al., 2015; Quattrini et al., 2020; Whelan et al., 2016) and across time on the scale of several months (Brown et al., 2020) to a year (Mulder et al., 2014). In the few studies that have assessed subfield reliability (Brown et al., 2020; Buser et al., 2020; Mulder et al., 2014), the majority appear to have moderate to good reliability, with the poorest reliability reported for the hippocampal fissure, which separates the dentate gyrus from the subiculum (Brown et al., 2020; Buser et al., 2020; Haładaj, 2020; Whelan et al., 2016). However, to our knowledge, day-to-day reliability, when a difference in hippocampal volume would be *least* expected, has not been evaluated. Moreover, reliability of hippocampal subfields has been predominately assessed in aging or healthy populations (Flores et al., 2015; Schmidt et al., 2018).

Herein, we examined the relationship between hippocampal subfield volumes and PTSD in a longitudinal study of psychological outcomes following a traumatic injury, using the probabilistic atlas-based procedure within *FreeSurfer* (version 6.0). As a secondary aim, we assessed the reliability of hippocampal subfield measurement. The participants in the study were scanned at three times, on two consecutive days approximately 2-weeks after their traumatic injuries (time 1: T1, and time 2: T2), and 6 months (time 3: T3) after their injury. This design allowed us to address four critical aims: 1) assess the reliability of hippocampal subfields on two consecutive days of scanning (T1 – T2), 2) determine whether hippocampal subfield measurements acutely post-trauma (T1) prospectively relate to future PTSD (T3), 3) examine the more routinely investigated cross-sectional association between subfield measurements at follow-up (T3) and current PTSD symptoms (T3), and 4) evaluate whether change in hippocampal volume (T1 – T3) relates to future PTSD symptoms (T3).

Based on the aforementioned research, we hypothesized that smaller global hippocampal volume (T1) would prospectively relate to T3 PTSD symptoms (Gilbertson et al., 2002; Gurvits et al., 2006; Kremen et al., 2012; Wang et al., 2010; Xie et al., 2018). We also hypothesized smaller global hippocampal volume (Apfel et al., 2011; Gurvits et al., 1996; Woon and Hedges, 2008), as well as smaller dentate gyrus/CA4 and CA1

Table 1
Sample Characteristics.

Variable	*Percent (%)*	*Mean*	*SD*	*Range*
Age (years)		33.1	10.8	
Sex				
Female	55%			
Race and Ethnicity				
African American/Black	60%			
White	26%			
More than one race/Other	8%			
Unknown/Not reported	6%			
Education				
Less than high school/GED	9%			
High school/GED	31%			
Some post-secondary education/college	25%			
Associate degree	14%			
Bachelor's degree or beyond	16%			
Not reported	5%			
Mechanism of Injury				
Motor Vehicle Crash	68%			
Assault/Altercation	13%			
Other (Fall, Pedestrian Struck, Crush Injury)	19%			
Days Since Injury				
T1		16.2	5.1	
T3		183.6	12.6	
CAPS-5 Total Symptom Severity ($N = 139$)		11.69	10.73	0–63
CAPS-5 PTSD Dx ($N = 139$)	18% ($N = 26$)			

Note: Demographic data presented for all participants with T1 Scans ($N = 197$); PTSD symptom severity is presented for subjects who completed T3 scans *and* the structured interview ($N = 139$). **CAPS-5**, Clinician Administered PTSD Scale for DSM-5.

(measured at T3) would be significantly related to T3 PTSD symptoms (Hayes et al., 2017). Finally, we anticipated there would be a significant change between T1 and T3 volumes, such that decreases in dentate gyrus and CA1 volume would track with PTSD symptoms (Chen et al., 2018; Hayes et al., 2017).

2. Method

2.1. Participants

Nine-hundred sixty-nine trauma survivors treated for their injuries at the Emergency Department (ED) at Froedtert Hospital (Milwaukee, Wisconsin, USA) were recruited for the *Imaging Study on Trauma & Resilience* (iSTAR study). Participants were recruited and screened for eligibility directly from the ED or by phone following discharge. After expressing interest in study participation, the participant received a complete verbal overview of the study and provided written informed consent. All procedures were approved by the Medical College of Wisconsin Institutional Review Board.

Of the 969 recruited for the study, 215 met eligibility criteria and were enrolled. Individuals were eligible if their trauma exposure met criterion A of PTSD diagnosis as defined by the *Diagnostic and Statistical Manual - 5th edition* (*DSM-5*; American Psychiatric Association, 2013), scored a minimum of three on the Predicting PTSD Questionnaire (Rothbaum et al., 2014; represents a greater risk of PTSD development), if they were English speaking, between the ages of 18–60 years, and able to schedule their first research visit within 30 days of their trauma. Exclusion criteria included contraindications for MRI scanning including metal objects or fragments in the body, claustrophobia, and pregnancy or planned pregnancy within the next 6 months, head injury more severe than a mild traumatic brain injury (score of less than 13 on the Glasgow Coma Scale; Sternbach, 2000), spinal cord injury with neurological deficit, self-inflicted injury, severe vision or hearing impairments, history of psychotic or manic symptoms, currently on antipsychotic medications, substance abuse noted in medical record, or on police hold following their injury. Sample characteristics are reported in Table 1.

2.2. Procedure

Participants attended research visits at three time points; within 2–3 weeks on two consecutive days (T1, T2) and 6 months (T3) following the trauma that resulted in their ED admission. At all visits, a large battery of behavioral and cognitive tasks, demographics, self-report questionnaires, physiologic, biologic, and neuroimaging data were collected. Here we report on select study measures and the structural MRI data from all time points. Of the 215 initially enrolled in the study, 208 were scanned at T1 (96.7% retention), 185 at T2 (86.0% retention), and 160 at T3 (74.0% retention). Reductions in sample sizes at each time point were the result of expected losses to follow-up due to scheduling conflicts or discontinued interest in study participation. However, final sample sizes in the reliability analyses were further reduced due to qualitative assessment of motion artifacts (i.e. large-scale ghosting, zippering, blurring, signal-dropout, etc.) within anatomical scans (usable scans: T1 = 197, T2 = 178, T3 = 153) or due to missing scans at relevant time points. Therefore, our final sample size for the T1 – T2 reliability analysis consisted of 175 with usable (motion artifact free) anatomical scans at both T1 and T2 (81.4% retention). Similarly, the final sample size for the analysis on T1 – T3 change over time and PTSD symptoms, as well as the T1 – T3 reliability analysis (included in Supplemental Material), included 141 participants with usable scans at both T1 and T3 (65.5% retention).

At T3, the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) was administered by a trained staff member to evaluate PTSD symptoms with respect to the index trauma (Weathers et al., 2018). CAPS-5 is considered the gold-standard of PTSD psychodiagnostic assessments and has good validity with other measures of PTSD and high internal consistency (Weathers et al., 2018). The interview consists of 30 items, with the first 20 corresponding to symptoms of PTSD included in the DSM-5 (American Psychiatric Association, 2013). The interviewer rated each symptom on severity and frequency, with individual item scores ranging from 0 to 4. A total PTSD symptom severity score was created by summing the first 20 items. In the current study, 20% of the CAPS were subject to reliability checks and the total symptom severity scores had excellent reliability (interclass correlation coefficient = 0.96, 95% Confidence Interval [0.93–0.98]).

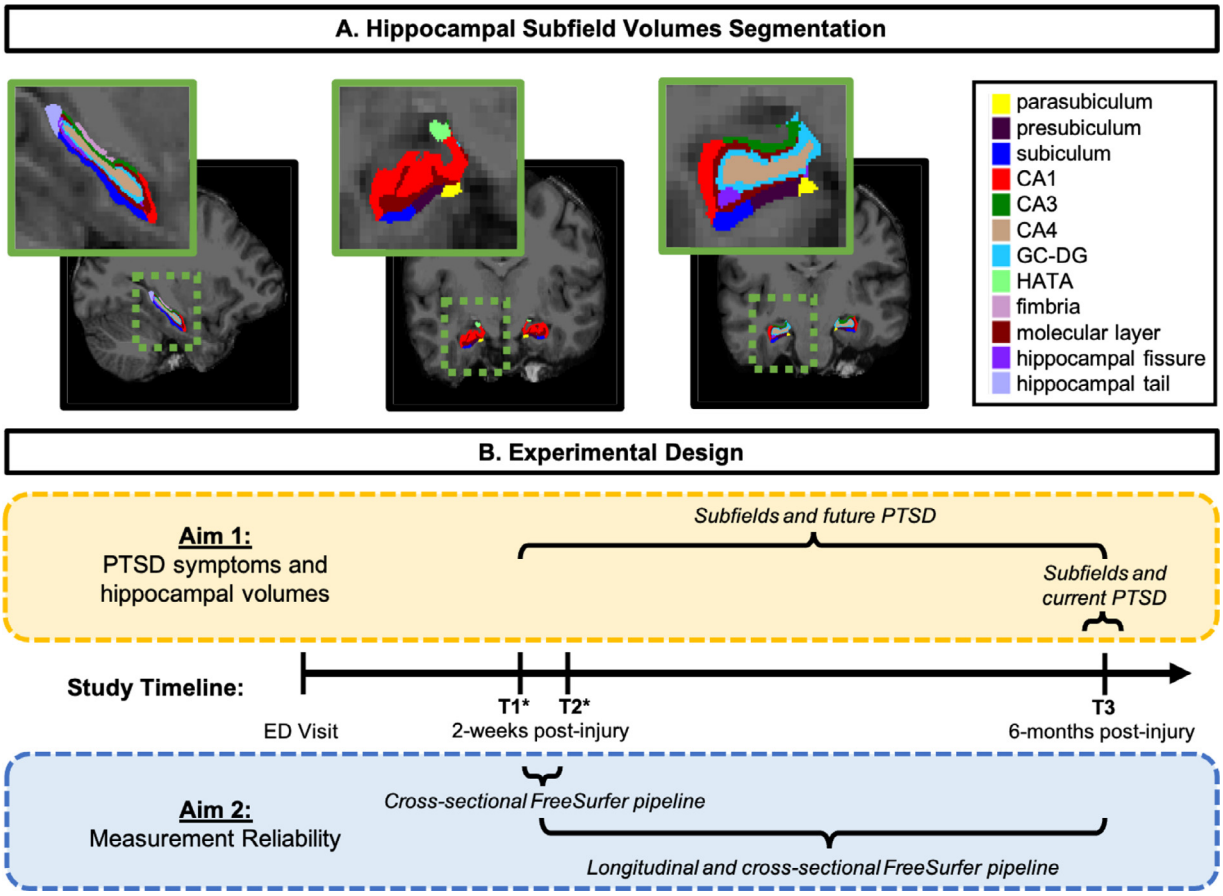

Fig. 1. A) Hippocampal subfield segmentations from a representative participant. **CA,** cornu ammonis; **GC-DG,** granule cell layer of the dentate gyrus; **HATA,** hippocampal-amygdaloid transitional area. B) Schematic of experimental design including the analytic strategy for Aim 1 (yellow box) and Aim 2 (blue box) as well as the study timeline. Following the participant's Emergency Department (ED) visit and recruitment into the study, MRI structural scans occurred at all study appointments: timepoint one (T1; two-weeks post-trauma), timepoint two (T2; two-weeks post-trauma), and timepoint three (T3; six-months post-trauma). *Note:* * T1 and T2 study appointments occurred on two consecutive days. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.3. MRI acquisition

Structural MRI scans were collected on one scanner: a 3.0T short bore GE Signa Excite system with a 32-channel head-coil. High resolution spoiled gradient recalled (SPGR) T1-weighted images were acquired in sagittal slices (voxel size=1 × 0.9375 × 0.9375 mm, TR=8.2 ms; TE=3.2 ms; FOV=240 mm; flip angle=12°, slice thickness=1 mm, # slices=150, matrix=150 × 256 × 256).

2.4. FreeSurfer processing pipeline

Anatomical T1-weighted scans from T1, T2, and T3 were all processed cross-sectionally in the *FreeSurfer* v6.0 *recon-all* pipeline for automated cortical and subcortical parcellations and tissue segmentation (https://surfer.nmr.mgh.harvard.edu/). The technical details of the pipeline have been described extensively in previous publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl, 2004; Fischl et al., 1999a,b, 2001, 2002, 2004; Fischl and Dale, 2000; Han et al., 2006; Jovicich et al., 2006; Reuter et al., 2010, 2012; Ségonne et al., 2004). Resultant reconstructions were visually inspected for quality control ensuring appropriate parcellations and segmentations were completed; however, no manual edits were made to limit experimenter bias (McCarthy et al., 2015). One subject was excluded from all analyses due to limited contrast resulting in poor reconstruction through the *FreeSurfer* pipeline (N = 175 for T1 – T2, N = 141 for T1 – T3).

As part of a supplemental analysis to compare reliability and performance of *FreeSurfer* processing pipelines, T1 and T3 (N = 141) scans were also processed through *FreeSurfer's* longitudinal processing stream (Reuter et al., 2010, 2012). Thus, hippocampal subfield volume reliability was compared between outputs from the cross-sectional and longitudinal processing streams (see Supplemental Material).

2.4.1. Hippocampal subfields

An automated pipeline for hippocampal subfield segmentation is included in *FreeSurfer* v6.0. This pipeline can be implemented on cross-sectional data and on the within-subject template from the longitudinal processing stream in *FreeSurfer*. The specific details of the steps within this pipeline are described in the original methods paper (Iglesias et al., 2015). Outputs from the analysis include volume estimates for each hemisphere of the following hippocampal subfields: hippocampal tail, subiculum, CA1, hippocampal fissure, presubiculum, parasubiculum, molecular layer, granule cell layer of the dentate gyrus (GC-DG), CA3, CA4, fimbria, hippocampal-amygdaloid transition area (HATA), and the whole hippocampus. See Fig. 1 for hippocampal subfield segmentation from a representative participant.

2.5. Statistical analysis

2.5.1. T1 – T2 hippocampal subfield measurement reliability: percent volume difference (PVD) and intraclass correlation coefficients (ICC)

Average percent volume difference (PVD, Eq. 1) was calculated as in Brown et al. (2020) and (Morey et al., 2009, 2010) for each hemisphere and each subfield to determine volumetric correspondence between T1

– T2 ($N = 175$).

$$\text{Percent Volume Difference} = \frac{|A - B|}{\left(\frac{A+B}{2}\right)} \times 100 \quad (1)$$

In a similar manner, intra-class correlation coefficients (ICC) were calculated to assess within-subject variability of hippocampal subfield measurement across time. Using the statistical package "irr" in R (Gamer et al., 2012), ICC $_{(3,1)}$ was used to estimate the agreement of hippocampal subfield measurements for T1 – T2 scans ($N = 175$). The ICC was modeled by a two-way mixed-effects model with random subject and fixed session effects. For both PVD and ICC, calculations for T1 – T2 were done using outputs from *FreeSurfer's* cross-sectional processing stream .

In addition, we explored reliability (PVD and ICC) of hippocampal subfield measurement between T1 – T3, without considering PTSD symptoms, using both the cross-sectional and longitudinal processing streams in *FreeSurfer*. The results of this analysis can be found in the Supplemental Material.

2.5.2. Hippocampal subfield volumes and PTSD symptoms

Of the 197 subjects with scans at T1, 30 did not complete the CAPS-5 at T3 and were therefore excluded from the analyses investigating PTSD symptoms. Thus, 167 individuals were included in the analysis examining T1 volumes and T3 PTSD symptoms and 139 subjects were analyzed in the tests assessing T3 volumes and T3 symptoms (two individuals who underwent T3 scanning did not complete the interview).

Bivariate relationships between PTSD symptom severity, age, and hippocampal subfields were first assessed using Pearson's correlations whereas the relationship between numeric variables and sex (coded "0" for males and "1" for females) were evaluated using point bi-serial correlation (see Supplemental Material). Considering we had no *a-priori* hypotheses regarding hemispheric differences, left and right hemispheres for each subfield, as well as whole hippocampus, were summed to yield a bilateral volume. In the primary analyses, general linear models were conducted to determine whether subfield volumes were prospectively related to T3 PTSD symptoms, or whether T3 subfield volumes were associated with T3 PTSD symptoms, after adjustment for sex, age, and total brain volume (total gray matter + total white matter). For all statistical tests, a Holm-Bonferroni correction was applied to correct for multiple comparisons (alpha=0.05; Holm, 1979).

2.5.3. Change in hippocampal subfield volumes and PTSD symptoms

Finally, we examined the relationship of PVD (Eq. 1) in hippocampal subfields across time (T1 – T3) in relation to future PTSD symptoms (T3). Of the 141 participants with scans at T1 and T3, 4 did not complete the CAPS-5 at T3, therefore 137 participants were included in this analysis. Left and right hemispheres for each subfield were summed to yield a bilateral PVD measure. Thirteen (12 subfields + whole hippocampus) general linear models (GLMs) were run with CAPS-5 (T3) as the dependent variable, and bilateral PVD of a given hippocampal subfield (T1 – T3) as the independent variable while controlling for sex, age, and total brain volume. For all statistical tests, a Holm-Bonferroni correction was applied to correct for multiple comparisons (alpha=0.05; Holm, 1979).

For this analysis, we used volume measurements from *FreeSurfer's* longitudinal processing stream; however, for completeness, we repeated the above analysis with volume measurements from the cross-sectional processing stream. Complete results for both versions of the analysis can be found in the supplement (Supplemental Table 4 and 5).

3. Results

3.1. PVD (T1 – T2)

Fig. 2 depicts average PVD for hippocampal subfield measurements acquired across two consecutive days (T1 – T2; $N = 175$). The subfields demonstrating highest consistency (PVD < 3%) included the molecular layer and whole hippocampal volume. The left fissure, bilateral parasubiculum, and HATA show the least consistency when processed showing approximately a 10% difference in volume across the two scans.

Results of the ICC analysis indicated good (between 0.75–0.9) to excellent (greater than 0.9; Koo and Li, 2016) scan-rescan reliability (ranged from 0.83 to 0.94) across the two consecutive scanning days using the cross-sectional processing stream (T1 – T2; Table 2).

Table 2
Intraclass correlations coefficients for hippocampal subfields (T1 – T2) processed through cross-sectional pipelines with 95% confidence intervals.

Subfield	Hemi	Cross-sectional		
		ICC	Lower bound	Upper bound
Hippocampal tail	L	0.91	0.88	0.94
	R	0.94	0.91	0.95
Subiculum	L	0.94	0.92	0.96
	R	0.92	0.89	0.94
CA1	L	0.93	0.90	0.95
	R	0.89	0.85	0.92
Hippocampal fissure	L	0.85	0.80	0.89
	R	0.83	0.77	0.87
Presubiculum	L	0.94	0.92	0.95
	R	0.91	0.87	0.93
Parasubiculum	L	0.88	0.84	0.91
	R	0.92	0.90	0.94
Molecular Layer	L	0.94	0.92	0.95
	R	0.90	0.86	0.92
GC-DG	L	0.93	0.90	0.95
	R	0.90	0.86	0.92
CA3	L	0.94	0.92	0.95
	R	0.91	0.88	0.93
CA4	L	0.91	0.89	0.94
	R	0.89	0.82	0.92
Fimbria	L	0.91	0.88	0.94
	R	0.94	0.91	0.95
HATA	L	0.89	0.85	0.91
	R	0.88	0.84	0.91
Whole hippocampus	L	0.94	0.91	0.95
	R	0.90	0.86	0.92

Hemi, hemisphere; **ICC,** intraclass correlation; **L,** left; **R,** right; **CA,** cornu ammonis; **GC-DG,** granule cell layer of dentate gyrus; **HATA,** hippocampal-amygdaloid transitional area, ***N* = 175.**

3.2. Hippocampal subfield volumes (T1) and future PTSD symptoms (T3)

Bivariate relationships between hippocampal subfields (T1), sex, age, and T3 CAPS-5 total scores are presented in Supplemental Table 1. Even before adjustment for multiple comparisons, none of the 12 subfield volumes were associated with T3 PTSD symptoms over and above total brain volume, age, and sex (Table 3; all full model uncorrected *p's* > 0.05; Hippocampal tail: $R^2 = 0.02$, $F(4, 162) = 0.87$, $p = .482$; Subiculum: $R^2 = 0.01$, $F(4, 162) = 0.52$, $p = .719$; CA1: $R^2 = 0.01$, $F(4, 162) = 0.68$, $p = .601$; Fissure: $R^2 = 0.01$, $F(4, 162) = 0.53$, $p = .707$; Presubiculum: $R^2 = 0.01$, $F(4, 162) = 0.683$, $p = .601$; Parasubiculum: $R^2 = 0.02$, $F(4, 162) = 0.86$, $p = .483$; Molecular Layer: $R^2 = 0.01$, $F(4, 162) = 0.67$, $p = .609$; GC-ML-DG: $R^2 = 0.02$, $F(4, 162) = 1.17$, $p = .323$; CA3: $R^2 = 0.02$, $F(4, 162) = 1.00$, $p = .405$; CA4: $R^2 = 0.03$, $F(4, 162) = 1.31$, $p = .267$; Fimbria: $R^2 = 0.01$, $F(4, 162) = 0.54$, $p = .701$; HATA: $R^2 = 0.01$, $F(4, 162) = 0.72$, $p = .573$). The whole hippocampus volume was not prospectively related to T3 PTSD symptoms, $R^2 = 0.01$, $F(4, 162) = 0.61$, $p = .654$.

T1 hippocampal subfield volumes separated by hemisphere were also examined. After correction for multiple comparisons, still no subfields were related to future symptoms.

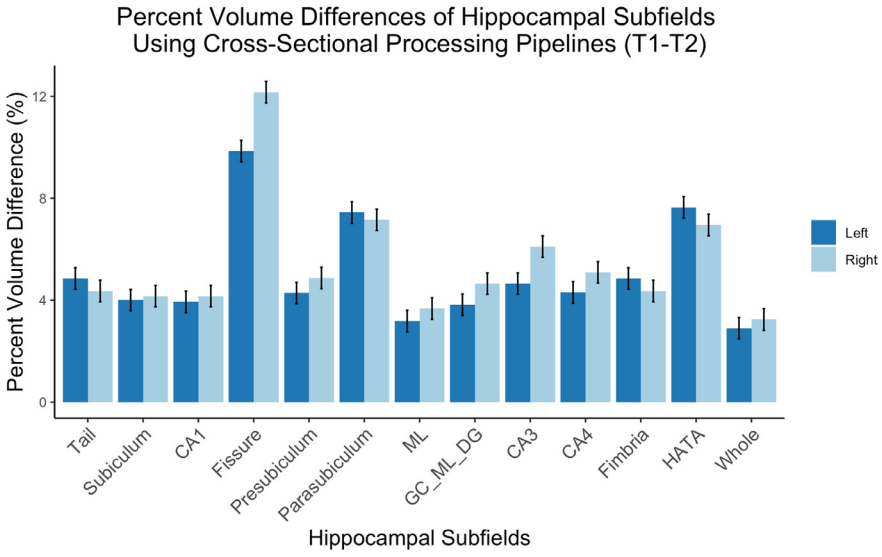

Fig. 2. Percent Volume Differences for all hippocampal subfields across two consecutive scan days (T1 – T2). Error bars represent standard error. **Left,** left hemisphere; **Right**, right hemisphere; **CA,** cornu ammonis; **ML,** molecular layer; **GC_ML_DG,** granule cell layer of the dentate gyrus; **HATA,** hippocampal-amygdaloid transition area; **Whole**, whole hippocampal volume. ***N* = 175.** *ICC (T1 – T2).*

3.3. Hippocampal subfield volumes (T3) associated with current PTSD symptoms (T3)

Bivariate relationships between hippocampal subfields (T3; obtained via cross-sectional pipeline), sex, age, and current PTSD symptoms are presented in Supplemental Table 2.

None of the subfields were associated with PTSD symptoms even before correction for multiple comparisons (all full model uncorrected *p's* > 0.05; Tail: R^2 = 0.03, $F(4, 134)$ = 1.22, p = .301; Subiculum: R^2 = 0.003, $F(4, 134)$ = 0.11, p = .976; CA1: R^2 = 0.005, $F(4, 134)$ = 0.18, p = .946; Fissure: R^2 = 0.003, $F(4, 134)$ = 0.11, p = .977; Presubiculum: R^2 = 0.005, $F(4, 134)$ = 0.19, p = .941; Parasubiculum: R^2 = 0.01, $F(4, 134)$ = 0.41, p = .801; Molecular Layer: R^2 = 0.006, $F(4, 134)$ = 0.23, p = .917; GC-ML-DG: R^2 = 0.01, $F(4, 134)$ = 0.547, p = .700; CA3: R^2 = 0.001, $F(4, 134)$ = 0.59, p = .667; CA4: R^2 = 0.01, $F(4, 134)$ = 0.563, p = .689; Fimbria: R^2 = 0.004, $F(4, 134)$ = 0.13, p = .968; HATA: R^2 = 0.007, $F(4, 134)$ = 0.24, p = .914), furthermore, whole hippocampus volume was not significantly associated with CAPS-5 scores, R^2 = 0.002, $F(4, 134)$ = 0.09, p = .983.

Again, we examined the same set of relationships separately for each hemisphere, still no subfield volumes at T3 were related to T3 PTSD symptoms after correction for multiple comparisons.

3.4. Change in subfield volume and PTSD symptoms

Full model results of the GLM analysis of subfield PVD (T1 – T3) associated with CAPS symptom severity (T3) using the longitudinal stream can be found in Supplemental Table 4. Results using the longitudinal stream outputs indicated there were differences in subfield significance (namely, bilateral fissure and subiculum); however, no results of this analysis survived correction for multiple comparisons using the Holm-Bonferroni method (all adjusted p > .80; Holm, 1979).

Though the primary evaluation in this analysis utilized the longitudinal stream outputs, examination of results using the cross-sectional stream outputs were also examined (Supplemental Table 5). No results of this analysis survived correction for multiple comparisons. Thus, in either analysis stream, change in hippocampal subfield volume over time (PVD T1 – T3) was not related to future PTSD symptoms (T3). When hippocampal subfield volumes were examined separately by hemisphere, for either cross-sectional or longitudinal stream, no changes in volumes were related to PTSD symptoms. Table 4

4. Discussion

We assessed the relationship between subfields and the development of PTSD symptoms and the stability of hippocampal subfield volumes after trauma in a traumatically injured sample. Our longitudinal design, which consisted of two consecutive scans acutely post-trauma (T1 and T2) and one scan 6-months post-injury (T3), provided a unique opportunity to evaluate measurement reliability and utilize both the cross-sectional and longitudinal processing streams within *FreeSurfer*. We found the associations (although nonsignificant after correcting for multiple comparisons) between subfields and PTSD symptoms varied depending on whether the measurement was acquired acutely post-trauma (T1) or at follow-up (T3) and whether the analysis used the cross-sectional or longitudinal pipeline.

Reliability between Tl and T2 scans of hippocampal subfields ranged from good to excellent, with all ICC values over 0.83 (Koo and Li, 2016). Change in volume did not significantly relate to future PTSD symptoms, therefore, we were also interested in measurement differences between T1 – T3. Reliability between T1 and T3 (Supplemental Material) also ranged from good to excellent with ICC values over 0.86 for both *FreeSurfer* processing streams (Koo and Li, 2016). In both sets of reliability analyses (T1 – T2 and T1 – T3), we replicated previous work showing excellent reliability in the whole hippocampus and the molecular layer (Brown et al., 2020) with poorer reliability in the hippocampal fissure (Quattrini et al., 2020). Percent volume difference metrics revealed similar outcomes; the lowest percent difference between T1 and T2 was in the whole hippocampus and molecular layer whereas the hippocampal fissure, HATA, and parasubiculum had the largest differences. Using the longitudinal preprocessing pipeline (T1 – T3) revealed the smallest percent differences; subfields demonstrating highest consistency (PVD < 3%) included the bilateral hippocampal tail, subiculum, CA1, molecular layer, and whole hippocampal volume. For both processing streams, the bilateral fissure, parasubiculum, and HATA showed the least consistency (PVD > 5%).

These results replicate and further support the reliability of *FreeSurfer* hippocampal subfield segmentation as demonstrated in other studies comparing varying sample sizes, scanners, and time intervals between scans (Brown et al., 2020; Whelan et al., 2016). Moreover, our traumatically injured sample yields a unique measurement of hippocampal volumes post-trauma that would not otherwise be reported in a healthy sample. Thus, reliable measurement across both sets of timepoints is important in disentangling volumetric differences in subfields

Table 3
Hippocampal volumes from *cross-sectional* processing stream (T1) and future PTSD Symptoms (T3).

Bilateral Subfield Volume (T1)		B	ß	T	*p*
Hippocampal Tail	(Intercept)	7.04	0.00	0.48	0.634
	Hippocampal Tail	0.01	0.10	1.22	0.224
	Sex	2.07	0.09	0.86	0.389
	Age	-0.07	-0.06	-0.75	0.455
	Total brain volume	-0.00	-0.02	-0.19	0.851
Subiculum	(Intercept)	14.00	-0.00	0.97	0.334
	Subiculum	-0.00	-0.03	-0.33	0.743
	Sex	2.31	0.10	0.96	0.337
	Age	-0.07	-0.06	-0.74	0.461
	Total brain volume	0.00	0.03	0.24	0.808
CA1	(Intercept)	15.25	-0.00	1.07	0.287
	CA1	-0.01	-0.08	-0.87	0.384
	Sex	2.24	0.09	0.94	0.350
	Age	-0.06	-0.05	-0.65	0.519
	Total brain volume	0.00	0.06	0.51	0.612
Hippocampal Fissure	(Intercept)	11.30	-0.00	0.78	0.438
	Hippocampal Fissure	0.01	0.03	0.42	0.679
	Sex	2.42	0.10	1.01	0.316
	Age	-0.07	-0.07	-0.83	0.409
	Total brain volume	0.00	0.01	0.06	0.953
Presubiculum	(Intercept)	16.30	-0.00	1.12	0.264
	Presubiculum	-0.01	-0.08	-0.87	0.383
	Sex	2.10	0.09	0.87	0.384
	Age	-0.07	-0.06	-0.76	0.446
	Total brain volume	0.00	0.05	0.47	0.642
Parasubiculum	(Intercept)	15.37	-0.00	1.09	0.278
	Parasubiculum	-0.07	-0.11	-1.22	0.225
	Sex	2.09	0.09	0.87	0.384
	Age	-0.06	-0.06	-0.70	0.484
	Total brain volume	0.00	0.05	0.51	0.611
Molecular Layer	(Intercept)	16.03	-0.00	1.11	0.270
	Molecular Layer	-0.01	-0.08	-0.85	0.399
	Sex	2.29	0.10	0.96	0.339
	Age	-0.06	-0.05	-0.67	0.503
	Total brain volume	0.00	0.06	0.52	0.604
GC-DG	(Intercept)	17.91	-0.00	1.26	0.211
	GC-DG	-0.03	-0.16	-1.64	0.103
	Sex	2.10	0.09	0.88	0.378
	Age	-0.04	-0.03	-0.40	0.690
	Total brain volume	0.00	0.11	0.93	0.356
CA3	(Intercept)	15.50	-0.00	1.10	0.272
	CA3	-0.03	-0.13	-1.42	0.157
	Sex	2.25	0.09	0.95	0.346
	Age	-0.04	-0.03	-0.42	0.675
	Total brain volume	0.00	0.07	0.68	0.500
CA4	(Intercept)	18.27	-0.00	1.28	0.201
	CA4	-0.04	-0.17	-1.80	0.074
	Sex	2.17	0.09	0.91	0.363
	Age	-0.03	-0.03	-0.37	0.710
	Total brain volume	0.00	0.11	0.97	0.335
Fimbria	(Intercept)	13.10	-0.00	0.93	0.352
	Fimbria	-0.02	-0.04	-0.45	0.650
	Sex	2.17	0.09	0.89	0.373
	Age	-0.07	-0.06	-0.80	0.424
	Total brain volume	0.00	0.03	0.25	0.799
HATA	(Intercept)	13.94	-0.00	0.99	0.322
	HATA	-0.07	-0.09	-0.96	0.337
	Sex	2.34	0.10	0.98	0.329
	Age	-0.03	-0.03	-0.36	0.718
	Total brain volume	0.00	0.06	0.53	0.594
Whole hippocampus	(Intercept)	15.82	-0.00	1.08	0.282
	Whole hippocampus	-0.00	-0.07	-0.68	0.496
	Sex	2.29	0.10	0.96	0.341
	Age	-0.06	-0.06	-0.68	0.497
	Total brain volume	0.00	0.05	0.44	0.659

Note. * **$p < .05$ uncorrected, CA,** cornu ammonis; **GC-DG,** granule cell layer of dentate gyrus; **HATA,** hippocampal-amygdaloid transitional area. **$N = 167$.**

Table 4
Hippocampal volumes from *cross-sectional* processing stream (T3) associated with current PTSD Symptoms (T3).

Bilateral Subfield Volume (T3)		B	ß	T	*p*
Hippocampal Tail	(Intercept)	10.66	-0.00	0.81	0.420
	Hippocampal Tail	0.01	0.20	2.15	**0.034**
	Sex	-0.55	-0.03	-0.24	0.811
	Age	-0.05	-0.05	-0.55	0.587
	Total brain volume	-0.00	-0.12	-1.05	0.294
Subiculum	(Intercept)	17.58	0.00	1.32	0.188
	Subiculum	-0.00	-0.04	-0.41	0.685
	Sex	-0.04	-0.00	-0.02	0.986
	Age	-0.04	-0.04	-0.41	0.684
	Total brain volume	-0.00	-0.01	-0.05	0.959
CA1	(Intercept)	17.92	0.00	1.36	0.177
	CA1	-0.01	-0.07	-0.65	0.514
	Sex	-0.08	-0.00	-0.04	0.971
	Age	-0.03	-0.03	-0.32	0.749
	Total brain volume	0.00	0.01	0.09	0.925
Hippocampal Fissure	(Intercept)	17.75	0.00	1.33	0.187
	Hippocampal Fissure	-0.01	-0.04	-0.39	0.699
	Sex	-0.13	-0.01	-0.06	0.956
	Age	-0.04	-0.04	-0.39	0.694
	Total brain volume	-0.00	-0.02	-0.21	0.831
Presubiculum	(Intercept)	18.47	0.00	1.39	0.168
	Presubiculum	-0.01	-0.08	-0.68	0.495
	Sex	-0.15	-0.01	-0.06	0.949
	Age	-0.04	-0.04	-0.41	0.682
	Total brain volume	0.00	0.02	0.12	0.907
Parasubiculum	(Intercept)	17.93	-0.00	1.37	0.173
	Parasubiculum	-0.07	-0.12	-1.15	0.250
	Sex	-0.17	-0.01	-0.07	0.941
	Age	-0.03	-0.03	-0.35	0.725
	Total brain volume	0.00	0.03	0.23	0.819
Molecular Layer	(Intercept)	18.32	0.00	1.38	0.168
	Molecular Layer	-0.01	-0.09	-0.80	0.427
	Sex	-0.00	-0.00	-0.00	0.998
	Age	-0.03	-0.03	-0.32	0.746
	Total brain volume	0.00	0.03	0.23	0.820
GC-DG	(Intercept)	18.65	-0.00	1.42	0.157
	GC-DG	-0.03	-0.17	-1.37	0.172
	Sex	-0.19	-0.01	-0.08	0.934
	Age	-0.01	-0.01	-0.12	0.903
	Total brain volume	0.00	0.08	0.59	0.556
CA3	(Intercept)	17.81	-0.00	1.37	0.174
	CA3	-0.03	-0.15	-1.44	0.153
	Sex	-0.06	-0.00	-0.03	0.980
	Age	-0.01	-0.01	-0.11	0.913
	Total brain volume	0.00	0.05	0.43	0.666
CA4	(Intercept)	18.41	-0.00	1.41	0.161
	CA4	-0.03	-0.16	-1.40	0.165
	Sex	-0.09	-0.00	-0.04	0.969
	Age	-0.01	-0.01	-0.14	0.892
	Total brain volume	0.00	0.08	0.57	0.571
Fimbria	(Intercept)	17.43	0.00	1.32	0.188
	Fimbria	-0.02	-0.05	-0.49	0.626
	Sex	-0.18	-0.01	-0.08	0.938
	Age	-0.04	-0.04	-0.50	0.616
	Total brain volume	-0.00	-0.02	-0.14	0.885
HATA	(Intercept)	16.81	-0.00	1.29	0.200
	HATA	-0.06	-0.09	-0.81	0.418
	Sex	0.03	0.00	0.01	0.989
	Age	-0.01	-0.01	-0.12	0.902
	Total brain volume	0.00	0.02	0.16	0.871
Whole hippocampus	(Intercept)	17.38	0.00	1.30	0.195
	Whole hippocampus	-0.00	-0.03	-0.28	0.783
	Sex	-0.01	-0.00	-0.01	0.995
	Age	-0.04	-0.04	-0.41	0.680
	Total brain volume	-0.00	-0.01	-0.08	0.936

Note. * **$p < .01$ uncorrected, CA,** cornu ammonis; **GC-DG,** granule cell layer of dentate gyrus; **HATA,** hippocampal-amygdaloid transitional area. ***N* = 139.**

attributed to trauma-related outcomes rather than measurement biases over time.

Decreased bilateral dentate gyrus/CA4 volume (T1) did not relate to greater PTSD symptom severity (T3). Though the dentate gyrus has been demonstrated to be associated with *current* PTSD symptoms (Hayes et al., 2017), our results suggest that, in this sample, the dentate gyrus is not prospectively related to, or associated with PTSD symptoms. The size of the dentate gyrus may not be predisposing of PTSD, rather it may be sensitive to the stress associated with PTSD in specific samples, particularly those that are comprised of highly symptomatic participants or individuals who experienced sustained trauma exposure (e.g., combat veterans; Zimmerman et al., 2016).

Chronic stress in the environment that individuals return to after trauma may impact hippocampal volumes (Haddad et al., 2015). The majority of neuroimaging work has been conducted with predominately White participants. Our sample is distinctly comprised of participants from diverse racial, ethnic, and socioeconomic backgrounds. As more data emerges on the neural impact of socioeconomic position (e.g., Johnson et al., 2016; Noble et al., 2012), racism and race-based stressors (Carter, 2007), and chronic exposure to environmental/societal stress (e.g., community violence, environmental toxins, etc.), we encourage future neuroscience research to consider how other forms of traumatic and stressful exposures (e.g., racism, sexism, poverty) may be impacting brain regions highly vulnerable to stress such as the hippocampus.

Previous work has demonstrated smaller whole hippocampus volume is associated with PTSD (e.g., Logue et al., 2018; Salminen et al., 2019; Xie et al., 2018). Surprisingly, we did not find a bivariate association between hippocampal volume and PTSD symptoms, nor was global hippocampal volume a significant term in the regression analysis. It is important to note that a number of studies have not demonstrated a relationship between whole hippocampal volume and PTSD (e.g., Bonne et al., 2001; Chen et al., 2018; see meta-analysis by Logue et al., 2018); perhaps indicating the association is not as robust as widely assumed and that trauma type and timing of measurement are important factors.

Our results, regardless of processing pipeline, do not clearly align with the framework describing differences in hippocampal subfields as either a vulnerability factor of PTSD development or as part of the subsequent post-trauma neurobiological changes. Rather, they suggest the two hypotheses may not be mutually exclusive. Our unique experimental design also stressed the importance of considering timing of structural measurements. The lack of consensus between our results and the majority of previously published findings (c.f. Bonne et al., 2001) is less surprising given a large recent study found that major depressive disorder, a common co-morbid diagnoses with PTSD, was a better predictor of hippocampal subfields than PTSD (Salminen et al., 2019). Future research should attempt to disentangle the effects of PTSD and depression on hippocampal structure and should extend research efforts across various post-trauma timepoints.

4.1. Limitations

Despite being a relatively large sample, the current results represent data from the same participants collected on the same scanner. To further validate the reliability of *FreeSurfer's* hippocampal subfield segmentation, larger samples should be collected on several scanners and with varying scan acquisition parameters. Greater resolution of anatomical scans would also likely enhance performance of the reconstruction pipeline. In addition, *FreeSurfer's* hippocampal subfield segmentation pipeline permits the inclusion of additional T2 weighted hippocampal scans to enhance segmentation reliability. Such scans were not collected in the current study and results still demonstrated reliable subfield estimation. However, future reliability examinations of this pipeline in *FreeSurfer* should include the additional T2 hippocampal scans.

The current sample was underpowered to investigate group differences (PTSD +/-) in hippocampal subfield volumes. Although participants in the current study were traumatically injured, the rates of PTSD (18% PTSD+) and PTSD symptoms in the sample are rather low (Mean CAPS-5 Total Severity = 11.77, $N = 140$). Similarly, the majority of the sample was injured in a motor vehicle crash yielding a sample less generalizable to samples with greater variability in trauma exposures (i.e., assault, combat, falls, etc.). Finally, we did not acquire a pre-trauma scan and therefore we were unable to explore whether differences in structure that predate the trauma can predict future trauma outcomes. The combination of these factors may explain the lack of replication of the well described smaller hippocampus and PTSD relationship (Hayes et al., 2017; Logue et al., 2018; Salminen et al., 2019). Though our reliability results closely resemble those reported from samples of healthy adults (Brown et al., 2020; Quattrini et al., 2020), and we excluded participants with head injury greater than mild TBI, using acute trauma survivors may confound hippocampal subfield reliability estimates as effects of physical trauma on volumes cannot be ruled out.

The hippocampus volume differences between individuals are relatively small. The average hippocampal reduction associated with a PTSD diagnosis is typically subtle, especially when trauma types are collapsed (mixed-trauma sample; Salminen et al., 2019). Coupled with the variability in measurement reliability, caution should be taken when interpreting only change in hippocampal subfields over time.

Conclusions

The current study demonstrated excellent reliability of *FreeSurfer 6.0* hippocampal subfield segmentation, on scans acquired on two consecutive days and six months apart, within a large trauma-exposed sample. Findings replicate and extend previous work examining *FreeSurfer* reliability by using a larger sample and time points not previously examined. Reliability of automated hippocampal subfield segmentations is crucial to research examining diseases and disorders affecting the hippocampus. Though ongoing validation is necessary, the current results contribute to the promise of robust methodology within *FreeSurfer* in examining brain-related changes associated with trauma exposure.

Although in our sample the hippocampal subfields volumes did not prospectively relate to or track with PTSD symptoms, future work should still consider how the function and structure of the distinct subfields may underlie pathogenesis of PTSD symptoms. Elucidating the role of hippocampal subfields in PTSD may lead to more effective treatments of specific symptoms (e.g., impaired extinction and over-consolidation of fear).

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Supplementary materials

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