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Posttraumatic stress disorder, social anxiety disorder and childhood trauma: Differences in hippocampal subfield volume

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ABSTRACT

Volume-based hippocampal findings in Social Anxiety Disorder (SAD) and Posttraumatic Stress Disorder (PTSD) have been inconsistent, with very little investigation of hippocampal subfields. We assessed the effects of early childhood trauma on hippocampal subfields in participants with SAD with and without early childhood trauma and PTSD, compared to healthy controls. The sample comprised 26 participants SAD with early childhood trauma, 22 participants with SAD without early childhood trauma, 17 with PTSD secondary to early childhood trauma and 25 control participants. We used Freesurfer version 6 to determine hippocampal subfield volumes. Findings included significant reduction in right parasubiculum volume between the PTSD group secondary to early childhood trauma and the SAD group without early childhood trauma, as well as a significant reduction in left HATA (Hippocampal Amygdala Transition Area) volume between PTSD with early childhood trauma compared to controls, as well as compared to SAD with early childhood trauma. These findings did withstand correction for multiple resting using the false discovery rate. Our findings of an association of reduced volumes in the parasubiculum and HATA regions with PTSD secondary to childhood trauma are interesting. Further work should investigate whether parasubiculum and HATA regional volume reductions in PTSD are a specific effect of early childhood trauma or a specific manifestation of PTSD pathology. Further work should also be undertaken to determine if hippocampal subfield atrophy is associated with SAD in the setting of early childhood maltreatment.

1. Introduction

Posttraumatic Stress Disorder (PTSD) and Social Anxiety Disorder (SAD) are debilitating disorders. Lifetime global prevalence rates for PTSD range from 2.3% in South Africa (Atwoli et al., 2013), 2.2% in Italy (Olaya et al., 2015; Carmassi et al., 2014), 1.3% in Japan (Kawakami et al., 2014) and 8.8% in Ireland (Olaya et al., 2015). For SAD the global prevalence rate is reported to be 4.0% and ranges from 5.5% in high-income countries to 1.6% in low/lower-middle income countries (Stein et al., 2017). Both PTSD and SAD are characterized by persistent detrimental effects on many life facets, including social dysfunction (Zatzick et al., 1997; Blanchard et al., 1998), work-related impairments (Blanchard et al., 1996; Davidson et al., 1991), and quality of life (Cloitre et al., 2005; Schneier et al., 1994). Childhood trauma is a common concomitant of both PTSD and SAD. In PTSD, childhood trauma represents an index developmental trauma that may additionally heighten the risk for the development of anxiety and mood disorders in adulthood (Koenen et al., 2007; Heim and Nemeroff, 2001; Pelcovitz et al., 1994; McCauley et al., 1997; Saunders et al., 1992). Albach and Everaerd (1992) documented that an estimated 60% of women who reported sexual abuse as children went on to develop PTSD as adults. Childhood trauma has also been found to increase the risk of developing SAD. Bandelow et al. (2004) compared childhood trauma rates in 50 participants with SAD and 120 healthy controls. Significant between-group differences were found, with the SAD group documenting significantly more sexual abuse, parental separation and familial violence compared to controls. Kuo et al. (2011) assessed the role of childhood abuse in 102 SAD participants compared to 30 healthy controls and reported that participants with SAD endorsed significantly more childhood emotional abuse and neglect. Further, emotional abuse and neglect, but not sexual or physical abuse or physical neglect, were associated with the severity of social anxiety.

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The effects of PTSD on hippocampal structure have been well documented. Logue et al. (2018) conducted the largest meta-analysis of the hippocampus and amygdala in 794 PTSD participants, representing a pooling of 16 cohorts. The authors sought out to assess eight different subcortical structures (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus & lateral ventricle). They found a statistically significant reduction of the hippocampus in subjects with PTSD compared to trauma-exposed controls.

There have been few neuroimaging studies of the hippocampus in SAD (social phobia) with findings being inconsistent. Irle et al. (2010) documented an 8% right hippocampal reduction in generalised social phobia (n = 24) compared to healthy controls (n = 24) and reported that volume reduction in the right hippocampus was directly related to disorder severity. Liao et al. (2011) reported decreased grey matter volumes in the parahippocampal gyrus in 18 SAD participants compared to the 18 matched healthy controls. However, Syal et al. (2012) documented no volumetric differences in the hippocampus in their study of 13 unmedicated participants with generalised SAD and 13 matched healthy controls. Further, Machado-Sousa et al. (2014), in 12 SAD participants, 12 participants with sub-threshold SAD and 12 healthy controls, found an enlargement of the hippocampus and amygdala in the SAD group compared to controls as well as an enlargement of the right hippocampus in participants with subthreshold SAD compared to controls.

1.1. Hippocampal sub-fields

The hippocampus is an area largely associated with long-term memory and also has connections with the limbic system which controls emotions (Ota et al., 2017). It is, however, not one large area, and can be subdivided into subfields, namely the Cornu Ammonis (CA) 1, CA 2 and 3 which are combined, CA 4, the hippocampal tail, subiculum, hippocampal fissure, presubiculum, parasubiculum, molecular layer, granule cell (GC) and molecular layers (ML) of the dentate gyrus (DG) or 'GCMLDG', fimbria, and the hippocampal amygdala transition area (HATA). Early preclinical investigation by Czeh et al. (2001) showed that prolonged exposure to stress resulted in atrophy in the DG of the hippocampus, while Sapolsky (2000), demonstrated that exposure to stress caused remodelling of the dendrites associated with the CA3 region, leading to atrophy.

1.2. Hippocampal subfields in childhood trauma

Studies documenting the specific impact of early childhood trauma on hippocampal subfields are few with only two published studies. Janiri et al. (2017) assessed the influence of childhood trauma, using the Childhood Trauma Questionnaire (CTQ), on hippocampal subfield volumes in participants with bipolar disorder and healthy controls. The authors found that childhood trauma was associated with a bilateral reduction in the subiculum, presubiculum and CA1 in healthy controls, compared to bipolar disorder participants. Teicher et al. (2012) examined the association of childhood maltreatment (which ranged from parental verbal aggression to familial sexual abuse) to hippocampal subfield volumes, specifically in the areas of DG (dentate gyrus) and CA3. The authors examined 193 unmedicated participants and found the strongest association between maltreatment and volumetric differences in the left CA2-CA3 and CA4-DG subfields. Interestingly, these findings were independent of a PTSD diagnosis, indicating that trauma exposure of itself was sufficient to lead to volumetric subfield reductions. Associations between maltreatment and the subiculum and presubiculum were also found, however these associations were not statistically significant.

1.3. Hippocampal subfields in PTSD

A number of studies of hippocampal subfield volumes in PTSD have been undertaken, with Wang et al. (2010) in a study of 17 male veterans with combat-related PTSD compared to 19 healthy controls, documenting significant reductions in the CA3 and dentate gyrus, and also total hippocampal reduction in veterans with PTSD compared to controls. Neylan et al. (2010) studied the effects of insomnia in 17 male veterans with PTSD compared to 19 matched healthy controls and found that a higher insomnia severity index (ISI) in participants, which was used as a measure of the severity of insomnia, was correlated with reduced hippocampal subfield volumes in the CA3 and dentate gyrus. Hayes et al. (2017) used Freesurfer to specifically examine the dentate gyrus in 97 war veterans, and found that the CA4/dentate gyrus was significantly reduced in PTSD. Averill et al. (2017) analysed hippocampal subfields in 68 veterans with PTSD compared to 36 control participants without PTSD using Freesurfer 6. PTSD severity was negatively correlated with the HATA region, while scores on the Beck Depression Inventory were significantly correlated with the dentate gyrus, CA4, HATA, CA2/3, molecular layer and CA1. Evidence from animal models suggests that subfields may be differentially affected by the type of psychopathology, for example Lucassen et al. (2006) showed that stress primarily affects the dentate gyrus, while in Alzeheimer's disease the CA1 region may be primarily impacted (West et al., 2004). This highlights the need to characterise and compare hippocampal subfield volumes across disorders.

1.4. Aim & hypothesis

In view of the inconsistent hippocampal volumetric findings in SAD and PTSD in the context of early childhood trauma, and because there has been no study comparing the effects of early childhood trauma in PTSD and SAD, we investigated and compared hippocampal subfields in individuals with PTSD secondary to early childhood trauma and in SAD both with and without early childhood trauma, compared to healthy controls. The availability of more up-to-date sMRI techniques permits the analysis of hippocampal subfield regions. Firstly, we hypothesised that individuals with PTSD, compared to all other groups would have significantly smaller hippocampal subfield volumes as has been documented in previous research, and specifically in the DG and CA3 (as these are areas that have been implicated in trauma). Secondly, we hypothesised that SAD participants with histories of early childhood trauma would demonstrate significantly smaller hippocampal subfields compared to SAD participants without histories of early childhood trauma. Finally, we hypothesised that women with early childhood trauma would demonstrate significantly smaller hippocampal subfield volumes compared to men with early childhood trauma, given sex differences in brain morphometry (Luders et al., 2002), and evidence indicating a susceptibility to the effects of early childhood traumatic events on hippocampal volumes in women (Bremner et al., 1999; Stein et al., 1995).

2. Methods

2.1. Participants

Participants were a convenience sample, selected from a study cohort investigating neurocognitive deficits in adults with SAD and PTSD with early childhood trauma. Ninety participants were included in the study: 26 with *SAD with early childhood trauma*, 22 participants with *SAD without early childhood trauma*, 17 with *PTSD secondary to early childhood trauma* and 25 age, gender and education matched control participants (without early childhood trauma exposure). Participation was completely voluntary, and written informed consent was obtained from all participants prior to undertaking any study-related procedures. A trained clinician psychologist (author DR) conducted informed consent, and diagnostic interviews with participants to determine the presence or absence of SAD, PTSD and early childhood trauma after which all participants underwent structural MRI scanning within two

Table 1
Demographic data.

	PTSD secondary to EDT (n = 17)	SAD with EDT (n = 22)	SAD without EDT (n = 26)	Controls (n = 25)	χ^2	p value
Gender						
Male	9	11	14	14	0.173	0.982
Female	8	11	12	11		
Age in years *Mean(SD)*	36.35(10.08)	35.59(9.26)	33.04(9.70)	30.48(7.33)	84.050	0.478
Ethnicity						
Black	5	3	0	4	20.543	0.015
White	7	2	5	5		
Coloured *	5	13	21	15		
Asian	0	4	0	1		
Education in years *Mean (SD)*	11.8 (3.26)	13.32 (2.19)	15.15 (3.40)	16.02 (3.25)	50.915	0.252
Marital Status						
Single	6	9	13	14	12.284	0.198
Married	6	10	9	6		
Living with a partner	2	3	3	5		
Divorced	3	0	1	0		
Employment						
Yes	14	14	21	17	2.864	0.413
No	3	8	5	8		

EDT = Early Developmental Trauma.
* Coloured = mixed race participants.

weeks of the diagnostic assessment.

2.2. Inclusion & exclusion

Both left and right-handed participants were included and matched across groups. Exclusion criteria were any DSM-IV psychotic disorder, bipolar mood disorder, obsessive-compulsive disorder, eating disorders, current alcohol or drug use disorders and any head injury resulting in a loss of consciousness. Other criteria for exclusion were drug abuse/dependence or alcohol abuse/dependence within the past 6 months. Participants on current psychotropic medication (with the exception of an SSRI [selective serotonin reuptake inhibitor]) were excluded. Two of the participants with PTSD were on SSRIs and were asked not to take their medication on the day of their MRI scans. Exclusions for MRI scanning were cardiac pacemakers, metal prostheses or pin(s), clips on blood vessels, inner ear prostheses, infusion pumps, metal intra-uterine contraceptive devices or pregnancy.

2.3. Data acquisition

Each scanning session lasted approximately one hour. Conventional structural data were acquired on a Siemens 3 Tesla Allegra MRI scanner at the Cape Universities Brain Imaging Centre (CUBIC at Tygerberg Campus). A high resolution T1-weighted 3D MPRAGE structural image was first obtained with the following parameters: sagittal orientation, TR = 2300 ms, TE = 3.93ms, FOV = 220 mm, 160 slices; 256 × 256 matrix; 1 × 1 × 1 mm^3 resolution; 9 min scan time. In addition to the structural scan, participants completed a spectroscopy (^{1}H-MRS) scan, and three functional MRI tasks testing emotional responses.

In order to acquire region specific brain volume measurements, we carried out further analysis using Freesurfer version 6, a brain imaging software package designed for the study of cortical and subcortical anatomy (Fischl and Dale, 2000). Aside from Freesurfer's processing stream which consists of several different stages: volume registration with the Talairach atlas, bias field correction, initial volumetric labeling, non-linear alignment to the Talairach space and final labelling of the volume (Dale and Fischl, 1999), the newest version allows for the specific processing of hippocampal subfields. This addendum to the Freesurfer processing stream was used to obtain hippocampal subfield values (Iglesias et al., 2015). A major benefit of Freesurfer is its ability to carry out all processing steps automatically, however its processing pipeline is computationally intensive; we, therefore, utilized custom batching scripts on the Centre for High Performance Computing (CHPC) in Rosebank, Cape Town (http://www.chpc.ac.za). Quality checking was carried out and no manual correction was needed.

2.4. Data analysis

We used SPSS version 25 to conduct MANCOVA (Multivariate Analysis of Covariance) to calculate the main effect volumetric differences from tests of between-subjects effects in hippocampal subfields across four groups – co-varying for age and intracranial volume (ICV). Correction for multiple comparisons of hippocampal subfields was done using the FDR (False Discovery Rate) which is less conservative approach but appropriate for exploratory analysis, and used a false discovery rate (FDR) of 0.5%. Further, we examined the interaction effects of hippocampal subfield volumes among trauma-exposed participants by gender using MANCOVA.

3. Results

3.1. Participant demographics

Scan data from 90 participants were analysed. The mean age for the PTSD group was 36.35 years (SD: 10.08), controls 30.48 years (SD: 7.32), SAD with trauma 35.59 years (SAD: 9.26) and SAD without trauma 33.04 years (SD: 9.70). The age range for the group as whole was 21–59 years, with 48 males and 42 females. For additional demographic information, please refer to Table 1.

3.2. Early childhood trauma

We used the Childhood Trauma Questionnaire (CTQ) to assess early developmental trauma (Bernstein and Fink, 1998; Bernstein et al., 1994). The CTQ assesses 5 subtypes of childhood trauma; emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. The most prevalent childhood trauma type was emotional abuse followed by emotional neglect (see Table 2), however a the early childhood trauma PTSD and SAD groups differed significantly on sexual abuse, physical abuse scores and CTQ total scores (Table 2). We ran a correlational analysis, covarying for age and ICV of hippocampal subfields and CTQ subscale and total scores for the early childhood trauma PTSD and SAD groups only. We found a significant correlation between the physical neglect score and the left fimbria (left p = 0.009; r = −0.424), in addition, the sexual abuse subscale was significantly correlated with the left HATA (p = 0.036; r = 0.346). See Table 3.

Table 2
Mean scores on the Childhood Trauma Questionnaire (CTQ).

	Emotional Abuse	Physical Abuse	Sexual Abuse	Emotional Neglect	Physical Neglect	CTQ Total
PTSD secondary to EDT						
Mean	17.71	13.59	11.88	16.71	10.94	70.82
SD	5.98	5.98	7.09	5.29	3.67	14.45
Controls						
Mean	6.40	5.92	5.40	6.76	5.52	30.00
SD	1.76	1.71	1.41	2.18	1.26	4.74
SAD with EDT						
Mean	16.68	9.91	6.86	14.73	8.59	56.77
SD	5.17	4.23	3.19	4.54	4.19	14.31
SAD without EDT						
Mean	11.24	8.48	6.90	11.32	7.44	33.92
SD	6.49	4.57	4.28	5.40	3.52	4.49
* **PTSD 2° to EDT *vs.* SAD with EDT**						
Mean Difference	17.13	11.51	9.05	15.59	9.62	**62.90**
SD	5.49	5.36	5.76	4.92	4.09	15.84
***p* value**	0.570	**0.031****	**0.005****	0.217	0.075	**0.004****

EDT – Early Developmental Trauma.
* Comparison between the PTSD and SAD with early childhood trauma groups.
** $p < 0.05$.

3.3. Hippocampal subfield volumes

Mean hippocampal subfield volumes are shown in Table 4, we calculated both adjusted and unadjusted p values. Adjusted p values showed a significant main effect for right parasubiculum (0.019) and left HATA (0.038). Tests of pairwise comparison were used to asses group by group hippocampal subfield differences using post-hoc comparison from Bonferroni correction, and found significant differences in the right parasubiculum between PTSD group secondary to early childhood trauma and SAD without early childhood trauma groups ($p = 0.022$), as well as differences in the left HATA between the PTSD group secondary to early childhood trauma and (i) the SAD with early childhood trauma ($p = 0.037$) group and (ii) the healthy control group ($p = 0.034$). Laterality is an area that has received some attention over the years with studies showing that the dysfunction of the hippocampus in PTSD is linked to the greater impairment in the left hippocampus (Menon et al., 2003; Choudhary et al., 2007). For all hippocampal subfields, there were no significant differences between the SAD groups with and without early childhood trauma for regional or total hippocampal volumes. Scatterplots showing the individual values for the two significantly reduced regions (RH parasubiculum and left HATA) by group are shown in Figs. 1 and 2. No gender differences in hippocampal subfields were found in the trauma exposed groups. See online supplement.

Table 3
Correlations (Spearman's rho) between CTQ and hippocampal subfield volumes in PTSD and SAD, with early childhood trauma, covarying for age and ICV (Intracranial volume).

	Emotional Abuse ($n = 39$) p (r)	Emotional Neglect ($n = 39$) p (r)	Physical Abuse ($n = 39$) p (r)	Physical Neglect ($n = 39$) p (r)	Sexual Abuse ($n = 39$) p (r)	CTQ Total ($n = 39$) p (r)
***LH* Hippocampal Tail**	0.780 (0.048)	0.747(0.055)	0.453(0.127)	0.785(−0.046)	0.527(−0.107)	0.784(0.047)
***RH* Hippocampal Tail**	0.613(0.086)	0.595(0.090)	0.626(0.083)	0.901(0.021)	0.361(0.155)	0.427(0.135)
***LH* Subiculum**	0.568(0.097)	0.381(0.381)	0.453(0.132)	0.758(−0.052)	0.184(−0.223)	0.829(0.037)
***RH* Subiculum**	0.558(0.099)	0.212(0.210)	0.731(0.058)	0.446(−0.129)	0.943(−0.012)	0.550(0.101)
***LH* CA1**	0.666(0.073)	0.964(−0.008)	0.756(0.0)	0.411(−0.139)	0.062(−0.310)	0.643(−0.079)
***RH* CA1**	0.937(0.014)	0.787(0.046)	0.723(−0.060)	0.360(−0.155)	0.4(−0.128)	0.679(−0.070)
***LH* Hippocampal Fissure**	0.093(0.280)	0.424(0.135)	0.280(0.183)	0.790(−0.045)	0.557(0.100)	0.179(0.226)
***RH* Hippocampal Fissure**	0.051(0.323)	0.072(0.300)	0.320(0.168)	0.592(0.091)	0.745(0.055)	0.064(0.307)
***LH* Presubiculum**	0.679(−0.070)	0.608(−0.087)	0.804(0.042)	0.397(−0.143)	0.526(0.108)	0.862(−0.030)
***RH* Presubiculum**	0.975(0.005)	0.718(−0.061)	0.712(0.063)	0.320(−0.168)	0.488(0.118)	0.909(0.019)
***LH* Parasubiculum**	0.270(−0.186)	0.707(−0.064)	0.608(−0.087)	0.499(−0.115)	0.921(−0.017)	0.427(−0.135)
***RH* Parasubiculum**	0.734(0.058)	0.604(0.088)	0.827(0.037)	0.358(−0.115)	0.371(0.151)	0.663(0.074)
***LH* Molecular Layer**	0.693(0.067)	0.917(0.018)	0.694(0.067)	0.468(−0.123)	0.217(−0.208)	0.885(−0.025)
***RH* Molecular Layer**	0.760(0.052)	0.686(0.069)	0.808(0.041)	0.484(−0.119)	0.581(−0.094)	0.941(0.013)
***LH* GC/ML/DG**	0.750(0.054)	0.896(0.022)	0.705(0.064)	0.544(−0.103)	0.112(−0.266)	0.790(−0.045)
***RH* GC/ML/DG**	0.641(0.079)	0.879(0.026)	0.844(−0.033)	0.350(−0.158)	0.209(−0.211)	0.704(−0.065)
***LH* CA3**	0.516(0.110)	0.836(0.035)	0.842(0.034)	0.587(−0.092)	0.245(−0.196)	0.971(0.006)
***RH* CA3**	0.976(0.005)	0.828(0.037)	0.930(−0.015)	0.416(−0.138)	0.231(−0.202)	0.617(−0.085)
***LH* CA4**	0.657(0.075)	0.700(0.065)	0.705(0.064)	0.660(−0.075)	0.136(−0.250)	0.967(−0.007)
***RH* CA4**	0.574(0.096)	0.816(0.040)	0.823(−0.038)	0.474(−0.121)	0.240(−0.198)	0.829(−0.037)
***LH* Fimbria**	0.901(0.021)	0.869(0.028)	0.490(−0.117)	**0.009*(−0.424)**	0.551(0.101)	0.710(−0.063)
***RH* Fimbria**	0.885(0.025)	0.858(0.093)	0.238(−0.199)	0.073*(−0.298)	0.248(0.195)	0.847(−0.033)
***LH* HATA**	0.612(0.086)	0.640(−0.079)	0.346(−0.160)	0.173(−0.229)	**0.036*(−0.346)**	0.183(−0.224)
***RH* HATA**	0.225(0.204)	0.446(0.129)	0.536(−0.105)	0.286(−0.180)	0.423(−0.136)	0.914(−0.018)
***LH* Total Hippocampus**	0.887(0.024)	0.833(0.036)	0.837(0.035)	0.560(−0.099)	0.261(−0.190)	0.844(−0.033)
***RH* Total Hippocampus**	0.692(0.067)	0.592(0.091)	0.964(0.008)	0.412(−0.139)	0.726(−0.060)	0.939(0.013)

LH – Left hemisphere; *RH* - Right hemisphere; CA1 - Cornu Amonis 1; GC/ML/DG - granule cell and molecular layers of the dentate gyrus; CA3 - Cornu Amonis 3; CA4 - Cornu Amonis4; HATA – Hippocampus Amygdala Transition Area.
* $p < 0.05$.

Table 4
Tests of between-subjects effects showing mean volumes (mm3) for hippocampal subfields after correcting for multiple testing (False Discovery Rate (FDR] using Benajmini-Hochberg [B-H] correction).

	PTSD (n = 17) Mean [95% CI]	SAD with early childhood trauma (n = 22)	SAD without early childhood trauma (n = 26)	Controls (n = 25)	Unadjusted p value	Adjusted p value (FDR)
***LH* Hippocampal Tail**	519.37 [483.63, 555.11]	525.87 [494.53, 557.22]	536.17 [507.56, 564.78]	536.87 [507.04, 566.71]	0.854	0.423
***RH* Hippocampal Tail**	539.68 [504.73, 574.64]	535.16 [504.12, 565.82]	547.47 [519.48, 575.45]	544.88 [515.70, 570.06]	0.941	0.5
***LH* Subiculum**	386.07 [361.73, 410.40]	407.13 [385.82, 428.50]	402.72 [383.24, 422.20]	404.05 [383.74, 424.37]	0.586	0.25
***RH* Subiculum**	385.85 [363.09, 408.61]	397.72 [377.76, 417.68]	400.73 [382.51, 418.95]	398.99 [379.99, 417.98]	0.765	0.384
***LH* CA1**	580.09 [544.43, 615.75]	616.93 [585.66, 648.21]	593.27 [564.72, 621.81]	598.15.77 [568.39, 627.92]	0.464	0.153
***RH* CA1**	599.28 [560.14, 638.43]	631.70 [597.38, 666.03]	631.19 [599.85, 662.52]	614.26 [581.58, 646.93]	0.530	0.211
***LH* Hippocampal Fissure**	138.64 [126.01, 151.27]	151.24 [140.17, 162.32]	143.88 [133.77, 153.99]	147.46 [136.92, 158.00]	0.482	0.173
***RH* Hippocampal Fissure**	132.02 [119.07, 144.97]	136.26 [124.91, 147.62]	133.01 [122.65, 143.38]	141.52 [130.71, 152.33]	0.637	0.346
***LH* Presubiculum**	292.15 [272.08, 312.22]	298.09 [280.48, 315.69]	310.33 [294.26, 326.40]	293.19 [276.44, 309.95]	0.406	0.134
***RH* Presubiculum**	275.69 [249.84, 301.54]	280.13 [257.54, 302.88]	304.04 [283.35, 324.73]	276.52 [254.94, 398.09]	0.204	0.115
***LH* Parasubiculum**	61.93 [53.32, 70.55]	63.15 [55.60, 70.70]	73.11 [66.22, 80.01]	61.95 [54.76, 69.13]	0.083	0.057
***RH* Parasubiculum**	56.96 [52.52, 61.41]	61.72 [57.82, 65.62]	65.56 [62.00, 69.11]	59.00 [55.29, 62.71]	**0.015***	**0.019****
***LH* Molecular Layer**	532.22 [502.21, 562.23]	557.61 [531.29, 583.93]	539.75 [515.73, 563.78]	544.56 [519.51, 569.61]	0.614	0.288
***RH* Molecular Layer**	546.25 [518.12, 574.39]	560.99 [536.32, 585.66]	556.46 [533.94, 578.98]	556.75 [533.27, 580.27]	0.885	0.461
***LH* GC/ML/DG**	282.63 [264.31, 300.95]	294.33 [278.26, 310.39]	288.82 [274.16, 303.49]	286.96 [271.67, 302.25]	0.806	0.403
***RH* GC/ML/DG**	288.93 [273.94, 303.92]	295.72 [282.57, 308.86]	284.70 [272.71, 296.70]	292.19 [279.68, 304.70]	0.646	0.365
***LH* CA3**	201.06 [185.03, 217.09]	216.18 [202.11, 230.24]	195.74 [182.91, 208.58]	209.25 [195.86, 222.63]	0.166	0.096
***RH* CA3**	215.19 [202.27, 228.12]	220.25 [208.92, 231.59]	203.25 [192.91, 213.60]	216.89 [206.10, 227.68]	0.132	0.076
***LH* CA4**	241.96 [227.15, 256.77]	253.48 [240.53, 266.43]	242.45 [230.63, 254.27]	247.70 [235.37, 260.02]	0.628	0.307
***RH* CA4**	251.74 [238.89, 264.60]	255.41 [244.13, 266.68]	244.75 [234.45, 255.04]	252.63 [241.89, 263.36]	0.540	0.230
***LH* Fimbria**	80.96 [72.45, 89.47]	85.03 [77.57, 92.49]	84.09 [77.28, 90.90]	83.72 [76.61, 90.82]	0.907	0.480
***RH* Fimbria**	81.30 [72.68, 89.92]	88.90 [81.35, 96.46]	85.13 [78.23, 92.03]	86.35 [79.15, 93.54]	0.612	0.269
***LH* HATA**	60.18 [55.02, 65.33]	69.55 [65.03, 74.07]	67.29 [63.16, 71.42]	69.44 [65.14, 73.75]	**0.029***	**0.038****
***RH* HATA**	60.78 [55.68, 65.89]	65.18 [60.70, 69.66]	64.89 [60.81, 68.98]	65.28 [61.02, 69.54]	0.514	0.192
***LH* Total Hippocampus**	3244.81 [3064.80, 3424.83]	3399.16 [3241.28, 3557.04]	3320.28 [3176.17, 34646.39]	3348.68 [3198.42, 3498, 94]	0.631	0.326
***RH* Total Hippocampus**	3308.00 [3140.19, 3475.80]	3397.89 [3250.72, 3545.05]	3384.20 [3249.87, 3518.54]	3382.96 [3242.88, 3523.03]	0.859	0.442

LH – Left hemisphere; *RH* - Right hemisphere; CA1 - Cornu Amonis 1; GC/ML/DG - granule cell and molecular layers of the dentate gyrus; CA3 - Cornu Amonis 3; CA4 - Cornu Amonis 4; HATA – Hippocampus Amygdala Transition Area.
Covariates: age, ICV (intracranial volume).
95% CI – 95% Confidence Interval.
FDR correction rate calculated at 0.5%.
* $p < 0.05$.
** B-H Correction adjusted p value (q) < 0.05.

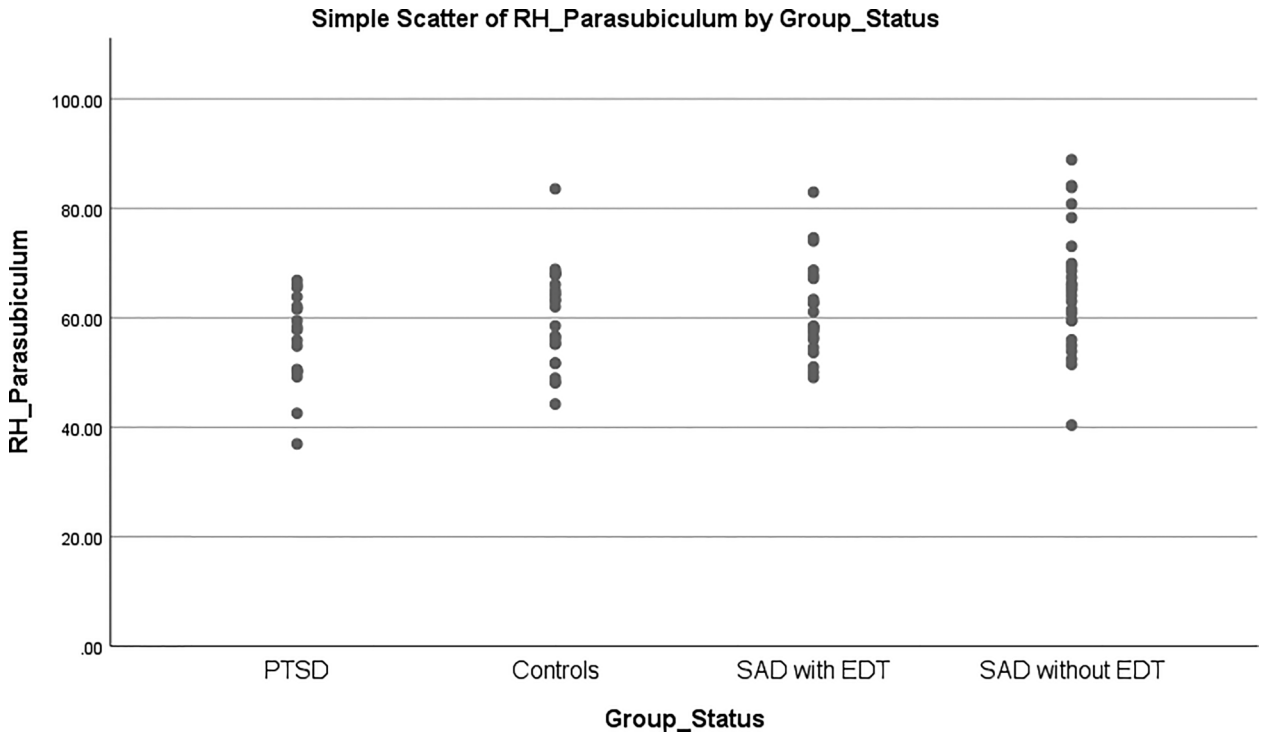

Fig. 1. Scatterplot showing individual values for the right parasubiculum by group.

4. Discussion

We found volumetric differences in the right parasubiculum and left HATA in the PTSD group with early childhood trauma compared to the SAD with early childhood trauma and control groups that were statistically significant, although there were no gender differences. These differences also withstood correction for multiple testing. One other study (Averelli et al., 2017) did find significant differences in the HATA in PTSD, however, this is the first known study to find hippocampal subfield differences in the parasubiculum in PTSD compared with SAD in the setting of early trauma. We did not find significant hippocampal subfield volume differences between the SAD with and without early childhood trauma groups.

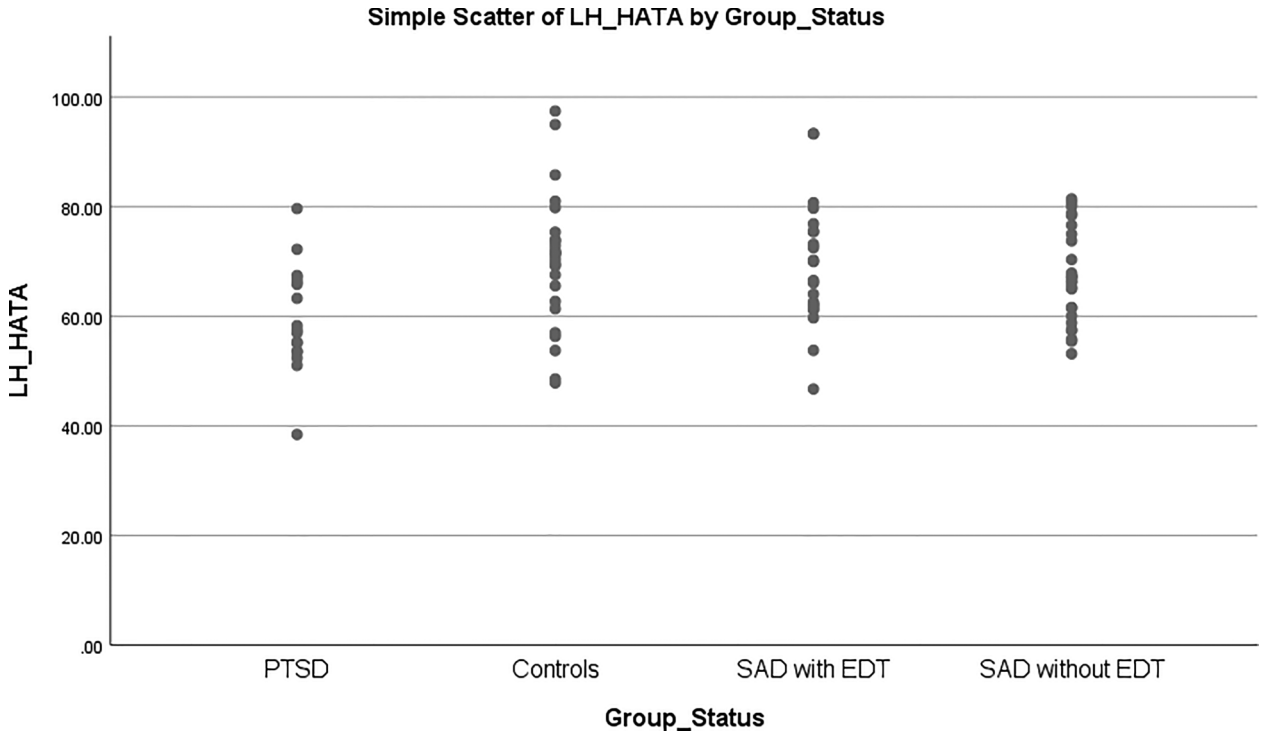

Fig. 2. Scatterplot showing individual values for the left hemisphere HATA by group.

4.1. HATA & parasubiculum

The HATA and parasubiculum were significantly reduced in the PTSD group compared to the other groups. The HATA is a region consisting both of the hippocampus and amygdala, anatomical components of the limbic system, and has often been investigated as a composite in volumetric studies (Shenton et al., 1992; Bogerts et al., 1993; Buchanan et al., 1993). It lies in the medial region of the hippocampus, and has interactions with other important areas such as the hypothalamus and prefrontal cortex. Averealli et al. (2017) concluded that alterations to the HATA may lead to a disruption to the processing and recalling of traumatic events. It has been postulated that any disruption to the HATA may disrupt the integrity of the hippocampus-amygdala-network, which could lead to a disruption in information processing (Foo et al., 2017) and affect the recall of traumatic events. The HATA has been involved in other conditions, such as Parkinson's disease (PD). Foo et al. (2017) studied 65 participants with PD, classified as having either no or mild cognitive impairment. They found reduced volume of the right HATA in PD participants, among other subfields (left fimbria and right CA1), and also found that volumes of the left HATA and left parasubiculum were predictive of a change from no cognitive impairment to mild cognitive impairment over time.

The parasubiculum has a key role in the processing of information, with axons from various brain regions (CA1 of the hippocampus and the amygdala) supplying the parasubiculum with nerves (van Groen and Wyss, 1990). The parasubiculum receives vital inputs from the amygdala (Canteras et al., 1992; Canteras et al., 1995; Pikkarainen et al., 1999). There has been little investigation of the parasubiculum in psychiatric disorders. One study that assessed the role between education and hippocampal subfields in Alzheimer's disease found reductions in the parasubiculum comes (Kang et al., 2018). In their study of 38 participants with mild cognitive impairment compared to 39 healthy controls, they found a significant correlation between education and the left parasubiculum, as well as other regions, including the presubiculum and subiculum in the mild cognitive disorder group compared to controls.

4.2. Type of abuse on brain morphometry

Teicher et al. (2016) in their review of the neurobiological effects of childhood abuse and neglect, found differential brain impacts based on type of trauma. We found significant correlations between physical neglect and the right parasubiculum and bilateral fimbria, and sexual abuse and the left HATA. This supports previous research that has found effects of early childhood trauma on hippocampal subfields (Teicher et al., 2012; Janiri et al., 2017).

CSA is associated with atrophy of limbic structures (the hippocampus and amygdala) (Vythilingam et al., 2002). Andersen et al. (2008) examined the effect of CSA on the hippocampus in 26 women with a past history of CSA, compared to 17 healthy controls. Their results revealed significant hippocampal reduction in participants with CSA, particularly when the abuse was carried out from the ages of 3-5 years and also from 11-13 years. Sheffield et al. (2013) examined the effects of CSA in 60 psychotic disorder patients, compared to 26 healthy control participants. They found total grey matter volume was correlated with the severity of CSA, but interestingly, this correlation was only present for CSA, not any other trauma (e.g. emotional/physical neglect).

4.3. Hippocampal subfields

Investigations of hippocampal subfield volumes in PTSD have been undertaken, with Chen et al (2018) examined hippocampal subfield alterations in PTSD. Their sample consisted of 282 military veterans with PTSD, compared to 142 trauma-exposed controls, and found significant differences between cases and controls in the left CA1 region only. Teicher et al. (2018) assessed the association of the number of types of trauma, and the severity and duration of abuse and hippocampal volume in 336 unmedicated participants, (132 males and 204 females). They found that hippocampal volume in males was predicted by neglect, not abuse, up until 7 years of age, whereas for females, it was abuse, not neglect that was predictive of hippocampal volume through the ages of 10-16 years. In our study, we found no significant of sex on the relationship between early childhood trauma and hippocampal subfield volumes, which may be partially explained by the fact that the majority of our participants suffered neglect, not sexual or physical abuse. The lack of significant group differences in DG and CA3 regions may also be explained by the fact that the majority of our participants suffered emotional neglect and abuse, and not physical or sexual abuse (Teicher et al., 2018) or adult onset trauma (Wang et al., 2010; Hayes et al., 2017; Chen et al., 2018), where DG. CA3 and CA1 subfield changes have been documented.

4.4. Limitations

Notable limitations are the sample size and the lack of a control group with early childhood trauma. The latter would have permitted an examination of the independent effects of childhood trauma on hippocampal subfield differences. In addition, we did not include a PTSD group with adult-onset trauma. Because of this, we are unable to separate out the effects of early vs adult onset trauma on these hippocampal subfield regions. The use of the CTQ to characterise childhood trauma is another limitation as it is a retrospective assessment that does not measure the duration of exposure nor the age of occurrence, variables that were not considered in this analysis. In view of the exploratory nature of the analyses, we did not adjust for multiple comparisons for the correlational tests of hippocampal subfields and CTQ subscale scores, which is a limitation. We included participants who were on SSRIs, of which there were only two (in the PTSD group). Additionally, we did not include a trauma exposed group without PTSD or SAD, to allow us to parse out trauma exposure from the disorder as the defining variable that is associated with hippocampal subfield reduction. Notwithstanding, these data add to our knowledge of hippocampal subfield volume differences in PTSD and SAD, with the findings requiring replication in other case-controlled studies.

Contributors

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Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.12.015.

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