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Psychosocial factors and hippocampal subfields: The Medea-7T study

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Abstract

Specific subfields within the hippocampus have shown vulnerability to chronic stress, highlighting the importance of looking regionally within the hippocampus to understand the role of psychosocial factors in the development of neurodegenerative diseases. A systematic review on psychosocial factors and hippocampal subfield volumes was performed and showed inconsistent results, highlighting the need for future studies to explore this relationship. The current study aimed to explore the association of psychosocial factors with hippocampal (subfield) volumes, using high-field 7T MRI. Data were from the Memory Depression and Aging (Medea)-7T study, which included 333 participants without dementia. Hippocampal subfields were automatically segmented from T2-weighted images using ASHS software. Generalized linear models accounting for correlated outcomes were used to assess the association between subfields (i.e., entorhinal cortex, subiculum, Cornu Ammonis [CA]1, CA2, CA3, dentate gyrus, and tail) and each psychosocial factor (i.e., depressive symptoms, anxiety symptoms, childhood maltreatment, recent stressful life events, and social support), adjusted for age, sex, and intracranial volume. Neither depression nor anxiety was associated with specific hippocampal (subfield) volumes. A trend for lower total hippocampal volume was found in those reporting childhood maltreatment, and a trend for higher total hippocampal volume was found in those who experienced a recent stressful life event. Among subfields, low social support was associated with lower volume in the CA3 ($B = -0.43$, 95% CI: −0.72; −0.15). This study suggests possible differential effects among hippocampal (subfield) volumes and psychosocial factors.

KEYWORDS
anxiety, depression, early life adversity, hippocampus, MRI, psychosocial

1 | INTRODUCTION

The hippocampus is implicated in many neuropsychiatric diseases, such as depression, schizophrenia, and dementia, where frequently a smaller hippocampal volume has been observed in comparing cases to controls. Based on animal studies, it is thought that the hippocampus is sensitive to stress and that the hippocampus mediates the stress response and release of glucocorticoids from the hypothalamic–pituitary–adrenal (HPA) axis (McEwen & Sapolsky, 1995). Chronic activation of the HPA axis due to stress or anxiety (Juruena et al., 2020) may lead to volume loss in the hippocampus, which has been demonstrated in studies assessing stressful events (Acosta et al., 2021; Papagni et al., 2011) and post-traumatic stress disorder (Ahmed-Leitao et al., 2016; Kitayama et al., 2005; Sapolsky et al., 1990).

However, the hippocampus is not a homogeneous structure. It is composed of multiple subfields that have shown differential responses to psychosocial factors. In previous animals studies, chronic stress has been shown to suppress neuronal development in the dentate gyrus (DG) and remodel dendrites in the cornu ammonis (CA), specifically in the CA3 (McEwen, 2002; Sapolsky et al., 1990). Further, neurogenesis inhibition in the DG has been related to psychosocial stress (Gould et al., 1997). This stress-specificity in hippocampal subfields has also been recently replicated in human studies as well (Dahmen et al., 2018; Mikolas et al., 2019; Teicher et al., 2012). However, regarding some psychosocial factors, such as social support, studies have mostly been limited to child or adolescent samples (Albaugh et al., 2017; Dahmen et al., 2018; Keresztes et al., 2020; Luby et al., 2019; Malhi et al., 2019; Malhi et al., 2020) and focused on total hippocampal volume rather than exploring the differential effect within subfields (Albaugh et al., 2017; Banning et al., 2020; Binnewies et al., 2021; Dahmen et al., 2018; Dannlowski et al., 2012; Gerritsen, van Velzen, et al., 2015; Keresztes et al., 2020; Malhi et al., 2019; Malhi et al., 2020). Further, these psychosocial factors, such as low social support (Miyaguni et al., 2021; Penninkilampi et al., 2018), depression (Byers & Yaffe, 2011; Diniz et al., 2013), anxiety (Kuring et al., 2020; Santabárbara et al., 2020), and childhood maltreatment (Radford et al., 2017), have been associated with an increased risk for incident dementia, which could possibly be mediated by hippocampal volumes (Gruenewald et al., 2020; Linnemann & Lang, 2020; Mah et al., 2016).

Therefore, by understanding the role psychosocial factors have on regions of the hippocampus in an adult population, we can better understand how these factors may contribute to the development of neurodegenerative diseases. Early-life stress has shown specific decline in the hippocampus (Whittle et al., 2013), as well as stunted hippocampal growth during adolescence (Paquola et al., 2017; Whittle et al., 2017), possibly due to programming effects in childhood resulting from an interplay of immune factors and hippocampal neurogenesis (Musaelyan et al., 2014). This highlights a possible importance of timing of stressful exposure in its influence on brain structure. Further, two reviews have highlighted that type of stressful exposure (e.g., emotional vs. physical abuse) may also have a differential effect on neurobiological alterations (Herzog & Schmahl, 2018; Teicher & Samson, 2016). However, exploring possible differences of timing (e.g., early- vs. late-life trauma) and type of exposure has yet to be assessed with hippocampal subfield volume.

To get a current overview of the literature, the first aim of the current study is to perform a systematic review of previous studies assessing psychosocial factors on hippocampal subfield volume in adults. The second aim is to examine the association between psychosocial factors and hippocampal (subfield) atrophy using high-field 7T MRI in a large sample. We hypothesized that psychosocial factors such as depression, childhood maltreatment, and anxiety would be associated with total hippocampal volume based on previous reviews (Geerlings & Gerritsen, 2017; Kolesar et al., 2019). We further hypothesized specific associations in the stress-sensitive DG and CA3 areas. Moreover, we hypothesized that lower social support would be negatively associated with hippocampal subfield volumes with no a-priori hypothesis on a specific subfield due to lack of previous research in adults.

2 | METHODS

2.1 | Participants

The Memory Depression and Aging (Medea)-7T study (Blom et al., 2020) is a cohort study at the University Medical Center (UMC) Utrecht with the aim to investigate risk factors and structural brain changes using 7T MRI in middle-aged and older adults with and without dementia. It is explained in-depth elsewhere (Blom et al., 2020). In brief, participants were recruited from the following settings: participants from the SMART-MR study ($n = 213$) (Geerlings et al., 2010), participants from the PREDICT-MR study ($n = 50$) (Wisse et al., 2015), participants 60 years or older without dementia from general practices ($n = 70$) (Blom et al., 2020), and patients with mild cognitive impairment or early Alzheimer's disease from memory clinics at the UMC Utrecht ($n = 35$) through the Utrecht Vascular Cognitive Impairment (VCI) Study group (see Acknowledgements) (Blom et al., 2020). Between January 2010 and October 2017, 368 participants underwent cognitive testing and MRI measurements. The 35 participants with mild cognitive impairment or dementia from the memory clinics were excluded. This left 333 individuals for the following analyses.

2.2 | Psychosocial factors

The following psychosocial factors were focused on in this study: depressive symptoms, anxiety symptoms, childhood maltreatment, recent stressful life events, and social support.

Depressive symptoms were assessed with the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) in the SMART-MR and PREDICT-MR cohorts and the Geriatric Depression Scale-15 (GDS-15) (Yesavage et al., 1982) in the general practices and memory clinics. Elevated depressive symptoms (yes/no) were defined as

scoring 6 or above on the PHQ-9 (Zuithoff et al., 2010) or on the GDS-15 (Pellas & Damberg, 2021; Pocklington et al., 2016). We chose a cut-off score of 6 or higher on the GDS-15 as it has been highlighted to have a higher sensitivity and specificity in community-based settings, as well as an overall higher specificity (Pocklington et al., 2016).

Anxiety was measured by the total score on the Beck Anxiety Inventory (BAI) (range: 0–63) (Fydrich et al., 1992) and dichotomized using population cut-offs (Karsten et al., 2011) of 11 and higher being classified as elevated anxiety symptomology.

Childhood maltreatment was measured with a selection of items from the NEMESIS Trauma Interview (Spijker et al., 2002) by a sum score of types of childhood maltreatment (i.e., emotional neglect, psychological abuse, physical abuse, and/or sexual abuse) that occurred before 16 years of age. Emotional neglect was described as not listened to, ignored, or unsupported. Psychological abuse was described as yelled at, insulted, unjustly punished/treated, threatened, belittled, or blackmailed. Physical abuse was defined as being kicked, hit, bitten, or hurt with an object or hot water. Sexual abuse was defined as any unwanted sexual experience. Childhood maltreatment was dichotomized as experiencing no childhood abuse or one or more type of abuse.

Recent stressful life events within the last 12 months were assessed via a questionnaire, including events such as serious illness to oneself or a close relative, job loss, and relational difficulties (Brugha et al., 1985). Stressful events were dichotomized as no recent event or one or more.

Social support was assessed via seven questions regarding perceived current social support (e.g., "There are people in my family and circle of friends who cheer me up"), on a scale of "incorrect", "partially correct", or "totally correct" (Stegenga et al., 2013). Scores ranged from 0–14, with high scores representing more support. Social support was categorized into low, medium, and high using a median cut-off. High social support was used as the reference.

For the PREDICT-MR and general practices, all psychosocial questionnaires were completed at the same time point as MRI collection. For the SMART-MR cohort, depression, anxiety, and recent stressful life events were all assessed at the same time point as MRI. However, social support and childhood maltreatment were assessed at an earlier time point, between 7 and 9 years before MRI collection.

2.3 | Demographics

Age and sex were self-reported through questionnaires.

2.4 | MRI assessment

Using a 7T MRI system (Philips Healthcare, Cleveland, OH) with a 32-channel receive head coil (Nova Medical, Wilmington, MA), 3D T1-weighted 3D T1-weighted (TI/TR/TE = 1225/4.8/2.2, acquired voxel size = 1.0 × 1.0 × 1.0 mm^3, reconstructed to 0.66 × 0.66 × 0.66 mm^3) and 3D T2-weighted (TR/TE = 3158/301, acquired voxel size = 0.70 × 0.70 × 0.70 mm^3, reconstructed to 0.35 × 0.35 × 0.35 mm^3) images were acquired. T1 and T2 images were reconstructed for nominal spatial resolution. The scanning duration was 10:15 min long per acquisition. To partly compensate inhomogeneity in the radio frequency field, a flip angle of 120° was performed. To reduce specific absorption rate and to optimize image contrast, a 12 to 90° tissue-specific refocusing pulse angle sweep was done (Busse et al., 2006). A field of view of 250 × 250 × 190 mm for foot-to-head × anterior-to-posterior × right-to-left was used. For more information regarding 7T sequence, please refer to (Wisse et al., 2014).

Conventional MR images were obtained using 1.5T (Gyroscan ACS-NT, Philips Medical System, Best, The Netherlands) in both the SMART-MR and PREDICT-MR studies. A sagittal 3D T1-weighted sequence (SMART-MR: TR/TE: 7.0/3.2 ms, voxel size = 0.94 × 0.94 × 1.00 mm^3 isotropic; PREDICT-MR: TR/TE: 6.9/1.3 ms, voxel size = 0.98 × 0.98 × 1.10 mm^3 isotropic) was acquired for segmentation of intracranial volume (ICV). MR images were collected using 3T MRI (Philips Medical Systems, Best, the Netherlands) for the participants from the general practices. This protocol included a sagittal 3D T1-weighted sequence (TR/TE = 8.0/4.5, voxel size = 1.00 × 1.00 × 1.00 mm^3 isotropic). Automatic brain segmentation was performed on the 3D T1-weighted sequence of the 1.5T or 3T images by CAT12 (version 1155), SPM12 (version 6906), and MATLAB (version 8.6). CAT12 segments gray matter, white matter, and cerebrospinal fluid. Total ICV was calculated as a sum of white and gray matter and CSF volumes. As segmentation on ICV has not yet been validated in the Automatic Segmentation of Hippocampal Subfields (ASHS, see next paragraph) on 7T, 1.5T or 3T images were used for ICV segmentation. Therefore, all participants underwent both a 7T MRI as well as a 1.5T or 3T MRI scan.

For hippocampal subfield segmentation, the ASHS software was used on the 3D T2-weighted images (UPenn, PA). ASHS differentiates between the CA1-3, CA4 and DG, subiculum, entorhinal cortex (ERC), and the hippocampal tail (Figure 1). The "UMC Utrecht 7T ASHS Atlas, compatible with original (slow) ASHS" was used from the ASHS atlases validated for 7T (Wisse et al., 2016). Using frequencies and histograms, segmentations were inspected for outliers. Manual, visual inspection was performed on outlier segmentations and then removed from the analysis if due to a segmentation error. Additionally, a random sample of 5% of all the segmentations were manually inspected for segmentation errors.

2.5 | Systematic review

On December 13, 2021, a PubMed search for psychosocial factors and hippocampal subfield volumes was performed (see Data S1). A total of 1554 articles were screened based on title/abstract. Seventy-eight articles were selected for full-text screening based on the inclusion criteria of assessing hippocampal subfield volume and assessing one or more of the relevant psychosocial factors. Systematic reviews or meta-analyses were not included. Articles were then selected for

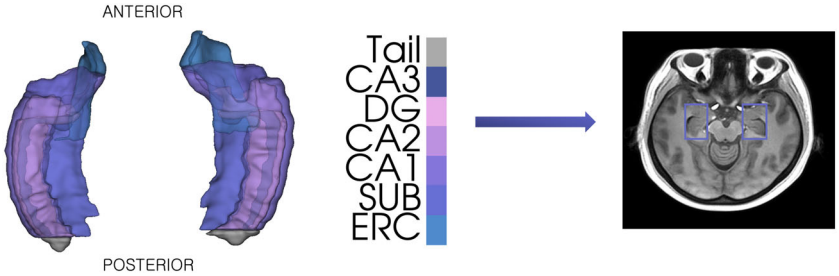

FIGURE 1 3D segmentation of hippocampal subfields using ASHS on a random participant for visualization, alongside an axial view of a template brain MRI. CA, Cornu ammonis; DG, dentate gyrus; SUB, subiculum; Tail, hippocampal tail; ERC, entorhinal cortex. For segmentation display, please see https://www.nitrc.org/projects/ashs

this review if (1) participants were 25 years or older (based on brain maturation in early adulthood [Sowell et al., 1999]), (2) participants were not cognitively impaired or diagnosed with any illness that was not major depressive disorder, an anxiety disorder, or post-traumatic stress disorder, (3) involved relevant psychosocial factors (i.e., depression, anxiety, childhood maltreatment or trauma, recent stressful life events, or social support), and (4) reported a cross-sectional association with hippocampal subfield volume. A total of 47 articles were included in this review.

2.6 | Data analysis

Multiple imputation was performed using the *mice* package in R (version 4.0.3) to address missing values (ranged from: 2.1% for BAI and 12.6% for the volumes of the hippocampal subfields) with 25 imputed datasets. The number of imputed datasets was chosen based on the percentage of non-complete cases (White et al., 2011) (e.g., if the complete case analysis is on 77% of the original N, then at least 23 imputed datasets are needed). Therefore, we chose 25 imputed datasets. Missing data on hippocampal subfield volume was due to the following: 11 individuals had no T1 or T2 available, 18 individuals had movement or signal interference, and 13 had a segmentation error. Predictive mean matching was used for continuous variables, polytomous logistic regression for unordered categorical variables, and logistic regression imputation for dichotomous variables. Left and right hemispheres of the hippocampal subfields were summed and converted into z-scores after imputation. The outcomes (i.e., hippocampal subfields) were also used in the prediction process for imputation as well as being imputed themselves. See Table S1 for descriptive statistics of both the complete case and imputed data.

Multiple linear regressions were fit for each psychosocial factor (i.e., depressive symptoms, anxiety symptoms, childhood maltreatment, recent stressful life events, and social support), adjusted for age, sex, and intracranial volume, on total hippocampal volume. Generalized linear models were fit for each psychosocial factor, also adjusted for age, sex, and intracranial volume, which included the unstructured correlation of each hippocampal subfield per individual (i.e., "a multivariate approach"), to assess differential effects between subfields. In these models, all hippocampal subfields are entered as one outcome, resulting in a single model per each psychosocial factor (see Code S1). Previous literature has shown that multivariate approaches increase the power of the model as well as reduce type I error compared with univariate approaches that ignore the correlation between outcomes (Mishra et al., 2021). While in univariate analyses, one can adjust the *p* value, the assumption of independence between outcomes is violated when they are correlated. Additionally, an exploratory analysis on types of childhood maltreatment was also performed for both outcomes: total hippocampal volume and hippocampal subfield volumes. The *nlme* package in R (version 4.0.3) was used for all multivariate models using the gls() function. Estimated marginal means from the multivariate models on subfield outcomes were computed using the *emmeans* package in R (see Code S1). Pooled results are shown. To correct for multiple testing, we defined statistical significance as $p < .005$ to account for the 10 tests performed (i.e., based on five separate predictors on two outcomes [i.e., total hippocampal volume and multivariate hippocampal subfields]). Lastly, sensitivity analyses were performed to explore possible differences when assessing type of childhood maltreatment, when using continuous data (i.e., BAI sum score, sum score on the stressful events questionnaire, and sum score on the social support questionnaire), when stratifying by cohort, when using a stricter cut-off of 10 (vs. six) or higher on the PHQ-9, when including all psychosocial factors in a joint model, and when excluding missing data (i.e., a complete case analysis).

3 | RESULTS

3.1 | Systematic review results

An overview of the literature review for psychosocial factors and their associations with hippocampal subfield volumes are displayed in Table 1. Of the 47 articles, 27 studies (57%) reported lower hippocampal subfield volumes in the presence of a psychosocial factor, specifically depression (Averill et al., 2017; Choi et al., 2017; Doolin et al., 2018; Frodl, Carballedo, et al., 2014; Frodl, Skokauskas, et al., 2014; Han et al., 2016; Han et al., 2019; Huang et al., 2013; Mikolas et al., 2019; Postel et al., 2021; Su et al., 2016; Travis et al., 2015; Treadway et al., 2015; Wisse et al., 2015; Zhou et al., 2020), anxiety (Takaishi et al., 2021), or childhood maltreatment or post-traumatic stress disorder (PTSD) (Aghamohammadi-Sereshki et al., 2021; Ahmed-Leitao et al., 2019; Averill et al., 2017; Chalavi et al., 2015; Chen et al., 2018; Hayes et al., 2017; Janiri et al., 2019; Lim et al., 2012; Luo et al., 2017; Postel et al., 2021; Wang et al., 2010; Yuan et al., 2020; Zhang et al., 2021). The most often affected subfields were the CA3 and DG. Most of the studies used

TABLE 1 Overview of literature researching the association between psychosocial factors and hippocampal subfield volumes

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Abbott, Jones (Abbott et al., 2014)	MDD	19 MDD + 20 HC	MDD: 65 (8) HC: 65 (9)	64	3T	CA1, CA2/3, DG, subiculum	Van Leemput et al., *Hippocampus* 2009	NA	No significant difference between MDD and HC.
Aghamohammadi-Sereshki, Coupland (Aghamohammadi-Sereshki et al., 2021)	MDD + childhood maltreatment	35 MDD + 35 HC	HC: 32 (10) MDD: 35 (9)	66	4.7T	CA1-3, subiculum, DG	Manual	ICV	CA1-3 had a negative correlation with childhood maltreatment in those with MDD.
Ahmed-Leitao, Rosenstein (Ahmed-Leitao et al., 2019)	Childhood maltreatment + PTSD + social anxiety disorder	26 SAD with trauma +22 SAD without trauma +17 PTSD +25 HC	PTSD: 36 (10) SAD w/ trauma: 36 (9) SAD w/o trauma: 33 (10) HC: 31 (7)	47	3T	All	Freesurfer	ICV	Negative correlation was found between physical neglect and left fimbria. A positive correlation was found with sexual abuse and the left HATA. Lower left HATA and right parasubiculum in PTSD group compared with the SAD and control groups.
Averill, Satodiya (Averill et al., 2017)	PTSD, BDI	36 PTSD, 32 combat control veterans	21–60	0	3T	Parasubiculum, presubiculum, subiculum, CA1, CA2/3, CA4, GC/DG, HATA, fimbria, molecular layer, hippocampal tail	Freesurfer	ICV	Total hippocampal volume negatively correlated with PTSD symptoms and BDI. PTSD negatively correlated with the HATA. BDI negatively correlated with the DG, CA4, HATA, CA2/3, molecular layer, and CA1.
Brown, Rutland (Brown et al., 2019)	MDD + depressive symptoms	24 MDD + 20 HC	MDD: 40 (10) HC: 40 (13)	58	7T	Subiculum, presubiculum, parasubiculum, CA1, CA3, CA4, GC of DG, ML DG, HATA, fimbria	Freesurfer	ICV	No differences in subfield volumes between groups. Positive associations were found for MDD severity and right CA1 and right CA3/4, but it did not survive multiple comparisons adjustment.

TABLE 1 (Continued)

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Burhanoglu, Dinçer (Burhanoglu et al., 2021)	MDD + depressive symptoms + anxiety symptoms	59 females high-risk for depression	23 (2)	100	3T	Fissure, tail, subiciulm, presubiculum, parasubiculum, CA1, CA3, CA4, ML, GC ML, fimbria, HATA	Freesurfer	ICV	No difference in subfields between those with MDD and those without MDD. No association with depressive or anxiety symptomology.
Cao, Passos (Cao et al., 2017)	MDD	152 HC + 86 MDD	HC: 35 (12) MDD: 41 (12)	67	1.5T	CA1, CA2/3, CA4, GCL, ML, presubiculum, subiculum, and tail	Freesurfer	ICV	No significant difference between MDD + HC.
Chalavi, Vissia (Chalavi et al., 2015)	PTSD + childhood maltreatment	16 PTSD +28 HC	HC: 42 (12) PTSD: 41 (12)	100	3T	CA1, CA2-3, CA4-DG, subiculum, presubiculum, fimbria	Freesurfer	TBV	No difference between PTSD and HC subfield volumes. Left CA1, CA2-3, CA4-DG, and presubiculum were negatively correlation with severity of childhood traumatizing events.
Chen, Sun (Chen et al., 2018)	PTSD	140 HC and 142 PTSD	HC: 39 (10); PTSD: 40 (10)	23	3T	CA1, CA3, CA4, DG, fimbria, fissure, HTA, molecular layer, parasubiculum, presubiculum, subiculum + tail	Freesurfer	HV	Lower subfield volumes associated with PTSD in left CA1 and bilateral CA3, only if hippocampal volume was included as a covariate.
Choi, Jung (Choi et al., 2017)	MDD, depressive symptoms	50 MDD + 50 HC	HC: 68 (4) MDD: 69 (7)	62	3T	CA1, CA2, CA3, CA4, DG, subiculum	ASHS	ICV	Bilateral CA1 and DG and right CA3 were smaller in the MDD group. Depressive symptoms were negatively correlated with left DG.
Doolin, Allers (Doolin et al., 2018)	MDD	74 MDD + 37 HC	HC: 31 (11) MDD: 33 (13)	60	3T	CA1-4, subiculum	Freesurfer	ICV	Hippocampal subfield volumes were smaller in MDD patients than HC for CA1 (left only), CA2/3 (left and right) and CA4 (right only).
Frodl, Carballedo (Frodl, Carballedo, et al., 2014)	MDD + childhood maltreatment	43 MDD + 43 HC	MDD: 41 (10) HC: 37 (13)	61	3T	CA1, CA2/3, CA4/DG, subiculum, presubiculum	Freesurfer	ICV	Patients with MDD had significantly smaller volumes of CA1, CA2/3, CA4/DG, and subiculum compared with healthy controls. Childhood maltreatment was not associated with any volumes.

(Continues)

TABLE 1 (Continued)

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Frodl, Skokauskas (Frodl, Skokauskas, et al., 2014)	MDD	38 MDD + 44 HC	MDD: 41 (11) HC: 36 (13)	63	3T	CA1, CA2/3, CA4/DG	Freesurfer	TBV	Patients with MDD had significantly smaller CA4/DG and CA2/3 volumes compared with healthy controls.
Han, Won (Han et al., 2017)	MDD	105 MDD + 85 HC	MDD: 43 (11) HC: 40 (14)	77	3T	CA1, CA2/3, CA4, granule-cell molecular layer of the DG, subiculum, presubiculum, fimbria, hippocampal fissure	Freesurfer	ICV	No differences between MDD and HC.
Han, Kim (Han et al., 2019)	MDD	102 MDD + 135 HC	MDD: 36 (11) HC: 36 (13)	58	3T	CA1, CA2/3, CA4, GCL, ML, presubiculum, subiculum, tail	From Iglesias et al.	ICV	MDD had lower volumes in the bilateral CA1, CA4, the granule cell layer, the molecular layer, the left CA2/3, and right presubiculum and subiculum compared with HC.
Han, Won (Han et al., 2016)	MDD	20 MDD + 21 HC	MDD: 42 (14) HC: 42 (10)	100	1.5T	CA1, CA2-3, CA4/DG, subiculum, presubiculum, fimbria, fissure	Freesurfer	ICV	Bilateral subiculum, left CA2-3, and left CA4/DG were smaller in MDD than in HC.
Hansen, Singh (Hansen et al., 2021)	MDD	30 MDD + 67 HC	MDD: 38 (16) HC: 54 (17)	43	3T	Hippocampal tail, subiculum, CA1, fissure, presubiculum, parasubiculum, molecular layer, DG, CA3, CA4, fimbria, HATA	Freesurfer	ICV	No significant difference between MDD + HC.
Hayes, Hayes (Hayes et al., 2017)	PTSD	97 recent war veterans	30 (7)	6	3T	CA4/DG, CA1, CA2/3, presubiculum, and subiculum	Freesurfer	ICV	CA4/DG was significantly smaller in veterans with PTSD compared with those without and scaled with PTSD symptom severity.
Hu, Zhang (Hu et al., 2019)	MDD	38 MDD + 55 HC	HC: 36 (15) MDD: 36 (12)	54	3T	Subiculum, presubiculum, CA1, CA2/3, CA4/DG, fimbria, hippocampal fissure	Freesurfer	ICV	No difference between MDD + HC.

TABLE 1 (Continued)

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Huang, Coupland (Huang et al., 2013)	MDD	20 MDD and 27 HC	HC: 33 (10) MDD: 35 (11)	62	4.7T	CA1-3, DG, subiculum	Manual	ICV	Total hippocampal volumes were smaller in unmedicated MDD participants than in controls or medicated MDD. Medicated MDD + controls did not differ from one another. CA1-3 was smaller in unmedicated MDD compared with controls. DG volume was also smaller in unmedicated MDD compared with controls + medicated MDD.
Janiri, Sani (Janiri et al., 2019)	Childhood trauma	81 controls	No trauma: 45 (16) Trauma: 46 (12)	57	3T	CA1, CA2/3, CA4/DG, presubiculum, subiculum	From Van Leemput et al. 2009 *Hippocampus*	ICV	Childhood trauma was associated with bilaterally smaller CA1, presubiculum, and subiculum volumes.
Kakeda, Watanabe (Kakeda et al., 2018)	MDD	40 MDD + 47 HC	HC: 41 (11) MDD: 47 (14)	38	3T	CA1, CA3, CA4, GC of DG, fimbria, subiculum, presubiculum, parasubiculum, ML, HATA, tail	Freesurfer	ICV	No difference between MDD + HC.
Kraus, Seiger (Kraus et al., 2019)	MDD	22 HC + 28 remitted MDD + 20 acute MDD	HC: 26 (7) rMDD: 27 (6) aMDD: 31 (10)	60	7T	CA1, CA3, CA4, fimbria, fissure, granule cell layer of the dentate gyrus, hippocampus–amygdala transition area, molecular layer, parasubiculum, presubiculum, subiculum, and tail	Freesurfer	TBV + GM	Right hippocampal fissure and right HATA were larger in remitted MDD compared to HC. Larger right subiculum values in both MDD groups compared with HC.
Lim, Hong (Lim et al., 2012)	MDD, depressive symptoms	30 MDD + 30 HC	HC: 72 (5) MD: 74 (6)	52	3G	CA1 CA2-3, CA4-DG, subiculum, presubiculum, fimbria, fissure	Freesurfer	ICV	Bilateral presubiculum, bilateral subiculum, left CA1, bilateral CA2-3, left CA4-DG, and bilateral fimbria smaller in MDD. No significant correlations between subfield volumes and depressive symptoms in those with MDD.

(Continues)

TABLE 1 (Continued)

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Lindqvist, Mueller (Lindqvist et al., 2014)	MDD	16 MDD + 19 HC	HC: 37 (12) MDD: 34 (7)	63	4T	CA1, CA1/2, CA3/DG, subiculum	From Mueller et al., 2007 *Human Brain Mapping*	ICV	No significant differences between MDD and control.
Liu, Pantouw (Liu et al., 2021)	MDD	35 MDD + 35 HC	HC: 43 (12) MDD: 43 (11)	69	1.5T	Presubiculum, subiculum, CA1, CA2-3, CA4/DG, fimbria, hippocampal fissure	Freesurfer	ICV	MDD patients had smaller volumes in left CA2/3 and CA4/DG. However, these did not remain significant after correction for multiple comparisons.
Luo, Liu (Luo et al., 2017)	PTSD	57 PTSD+ + 11 PTSD- + 39 HC	PTSD+: 57 (6) PTSD-: 58 (7) HC: 56 (6)	58	3T	CA1, CA2/3, CA4/DG, subiculum, presubiculum, and fimbria	Freesurfer	ICV	PTSD+and PTSD- group had smaller CA2-3, CA4/DG, subiculum volumes than HC.
Maller, Broadhouse (Maller et al., 2018)	MDD	202 MDD + 68 HC	HC: 30 (13) MDD: 33 (13)	52	3T	CA1, CA2/3, CA4, DG, HATA, fimbria, alveus	Freesurfer	TBV + THV	Larger hippocampal tail in those with MDD. Uncorrected, associations were also found for the molecular layer, the granule cells of the molecular layer, the CA2/3 + CA4, and the combine alveolus/fimbria, with lower volumes in MDD except for higher volumes in the fimbria/alveolus.
Mikolas, Tozzi (Mikolas et al., 2019)	Childhood maltreatment and MDD	85 MDD and 67 HC at two sites	HC, CAMI = 37 (13); MDD, CAMI = 40 (9); HC, TCIN = 34 (11); MDD, TCIN = 38 (13)	74	3T	CA1, CA3, CA4, fimbria, sum of granular layer and dentate gyrus, hippocampus-amygdala-transition-area, hippocampal fissure, molecular layer, hippocampal tail, parasubiculum, presubiculum, subiculum	Freesurfer	TBV	Those with MDD had smaller CA1, CA3, CA4, granular layer + dentate gyrus, and molecular layer. The whole hippocampus was also smaller in those with MDD compared with HC. In patients with ELA, larger volumes were found in the CA1, CA3, and ML compared with MDD patients without ELA.

TABLE 1 (Continued)

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Na, Won (Na et al., 2018)	MDD	47 MDD + 30 HC	MDD: 45 (11) HC: 44 (13)	100	3T	CA1, CA3, CA4, molecular layer, granule cells, subiculum, presubiculum, parasubiculum, HATA	Freesurfer	ICV	No differences between MDD and HC in subfield volume.
Na, Chang (Na et al., 2014)	MDD	45 MDD + 72 HC	MDD: 42 (12) HC: 41 (14)	73	3T	CA1, CA2/3, CA4/DG, subiculum, presubiculum, fimbria, fissure	Freesurfer	ICV	No differences between MDD and HC in subfield volume.
Ota, Sato (Ota et al., 2017)	MDD	36 MDD + 35 HC	MDD: 38 (11) HC: 39 (13)	47	3T	CA, DG, subicul	ASHS	ICV	No difference between MDD + HC.
Postel, Mary (Postel et al., 2021)	PTSD + trauma exposure + depressive symptoms	53 trauma-exposed with PTSD +39 trauma-exposed without PTSD +80 HC	PTSD+ = 37 (9) PTSD- = 36 (7) Non-exposed = 32 (12)	53	3T	CA1, CA2-3/DG, subiculum, tail	ASHS	ICV	Smaller volumes of the CA1 and the CA2-3/DG were found in the PTSD group compared with those without PTSD but trauma-exposed. There were no differences between those exposed to trauma and those unexposed. CA2-3/DG region was negatively associated with depressive symptoms.
Szymkowicz, McLaren (Szymkowicz et al., 2017)	Depressive symptoms	48 community-dwelling adults	69 (7)	70	3T	CA1, CA2-3, subiculum	Freesurfer	ICV	No main effects of depressive symptoms of hippocampal subfield volume.
Su, Faluyi (Su et al., 2016)	MDD	5 MDD+ 13 HC	MDD: 73 (5) HC: 68 (6)	61	3T	CA1, CA2, CA3/DG, subiculum	Manual	N/A	MDD had smaller volumes in the CA1 and subiculum.
Takaishi, Asami (Takaishi et al., 2021)	Panic disorder + symptoms	38 PD + 38 HC	PD: 39 (10) HC: 38 (10)	66	1.5T	Presubiculum, CA1, CA2/3, fimbria, subiculum, CA4/DG	Freesurfer	ICV	PD had smaller right CA2/3 than HC. No association between subfields and symptom severity.
Tannous, Godlewska (Tannous et al., 2020)	CTQ, BDI, HAM-D, STAI	46 HC + 71 MDD	HC = 32 (11), MDD = 32 (10)	55	7T	All	Freesurfer	ICV	No group differences in any subfields. No association between any subfield and CTQ score, illness duration, or mood rating scale.
Taylor, Deng (Taylor et al., 2020)	MDD	59 MDD + 21 HC	66 (6)	62	3T	CA1-3, CA4/DG, subiculum	ASHS	ICV	No differences between MDD + HC.

(Continues)

TABLE 1 (Continued)

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Travis, Coupland (Travis et al., 2015)	MDD	15 MDD and 15 HC	HC = 33 (10); MDD = 36 (9)	63	4.7T	CA1-3, DG	Manual	ICV	No difference between MDD and HC in hippocampal volume. MDD patients showed smaller DG volumes compared with HC. Duration of depression negatively correlated with total HV and CA1-3 and DG subfields.
Travis, Coupland (Travis et al., 2016)	MDD	14 MDD + 14 HC	HC: 33 (10) MDD: 36 (9)	73	4.7T	CA1-3, DG, subiculum	From Malykhin et al., 2010 *Neuroimage*	ICV	No significant differences between MDD and controls. No significant correlations between depressive symptoms and hippocampal subfield volume.
Treadway, Waskom (Treadway et al., 2015)	MDD	51 HC + 52 MDD	HC: 37 (13) MDD: 41 (13)	52	1.5T	CA1, CA2/3, CA4/DG, stratum, subiculum	Multiple Automatically Generated Templates for different Brains (MAGeT Brain)	ICV	DG was associated with a significant reduction in volume as the number of episodes increased in all subjects. In MDD, significant reductions were seen across all subfields.
Wang, Neylan (Wang et al., 2010)	PTSD	17 PTSD +19 HC	41 (12)	0	4T	Entorhinal cotex, subiculum, CA1, CA3/DG	From Mueller et al., 2007 *Neurobiol Aging*	ICV	CA3/DG was smaller in PTSD than in the controls.
Weis, Webb (Weis et al., 2021)	PTSD	215 trauma survivors	33.1 (10.8)	55	3T	Hippocampal tail, subiculum, CA1, hippocampal fissure, presubiculum, parasubiculum, molecular layer, granule cell layer of the dentate gyrus, CA3, CA4, fimbria, hippocampal-amygdaloid trainsition area, and whole hippocampus	Freesurfer	TBV	There was no relationship found cross-sectionally or longitudinally on PTSD symptoms and subfield volumes.

TABLE 1 (Continued)

Author	Psychosocial factor	Design and study population	Age (years)	Sex, female (%)	MRI field strength	Subfields	Segmentation method	ICV/TBV covariate	Results
Wisse, Biessels (Wisse et al., 2015)	Major depressive episodes	47 participants from GP attendees, no MDE = 34, ever MDE = 13.	60 (10)	62	7T	Subiculum, CA1, CA2, CA3, DG + CA4, total hippocampus, ERC	Manual	ICV	All subfields except the CA3 were significantly smaller in the ever MDE group.
Yuan, Rubin-Falcone (Yuan et al., 2020)	MDD + childhood maltreatment	44 HC + 17 abused MDD + 24 non-abused MDD	HC: 33 (12) MDD: 35 (11)	59	3T	CA1, CA3, DG, subiculum, parasubiculum	Freesurfer	ICV	No differences in subfields between MDD + HC. Smaller volumes of the left CA1 were found in those abused with MDD compared with those without abuse.
Zhang, LuZhang et al., (2021)	PTSD	145 survivors of a major earthquake and 56 HC	PTSD: 43 (10); TC: 44 (9); HC 40 (12)	67	3T	CA1, CA2/3, CA4, molecular + granule layers of the DG, molecular layer, subiculum, presubiculum, parasubiculum, fimbria, fissure, and HATA	Freesurfer	ICV	The total hippocampus was smaller in both PTSD and trauma-exposed groups compared with HC. Smaller volumes were also found in the CA3, CA4, DG, subiculum, and presubiculum.
Zhou, Wu (Zhou et al., 2020)	MDD	44 MDD + 45 HC	MDD: 35 (12) HC: 33 (11)	59	3T	CA1, CA3, CA4, fimbria, GC + ML DG, HATA, fissure, tail, ML, parasubiculum, presubiculum, and subiculum	Freesurfer	ICV	MDD had smaller left CA1, CA4, GC ML DG, HATA, and ML, and right GC ML DG, and subiculum.

Abbreviations: ASHS, Automatic Segmentation of Hippocampal Subfields; BDI, Beck Depression Inventory; CA, Cornu Ammonis; CTQ, Childhood Trauma Questionnaire; DG, dentate gyrus; ERC, entorhinal cortex; GC, granule cell; GM, gray matter; HAM-D, Hamiltor Depression Rating Scale; HATA, hippocampal amygdala transition area; HC, healthy control; HV, hippocampal volume; ICV, intracranial volume; MDD, Major Depressive Disorder; MDE, mild depressive episode; ML, molecular layer; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; STAI, State Trait Anxiety Inventory; TBV, total brain volume.

1.5T or 3T MRI, with four studies (9%) using high-field 7T MRI (Brown et al., 2019; Kraus et al., 2019; Tannous et al., 2020; Wisse et al., 2015). Twenty-four studies (51%) reported no significant differences in volume (Abbott et al., 2014; Brown et al., 2019; Burhanoglu et al., 2021; Cao et al., 2017; Chalavi et al., 2015; Frodl, Carballedo, et al., 2014; Han et al., 2016; Hansen et al., 2021; Hu et al., 2019; Kakeda et al., 2018; Lim et al., 2012; Lindqvist et al., 2014; Liu et al., 2021; Na et al., 2014; Na et al., 2018; Ota et al., 2017; Postel et al., 2021; Szymkowicz et al., 2017; Tannous et al., 2020; Taylor et al., 2020; Travis et al., 2015; Travis et al., 2016; Weis et al., 2021; Yuan et al., 2020), and four studies (9%) found increased volumes, specifically in the left hippocampal amygdala transition area (HATA) for sexual abuse (Ahmed-Leitao et al., 2019), the hippocampal tail in those with major depressive disorder (MDD) (Maller et al., 2018), the CA1, CA3, and molecular layer in those with childhood maltreatment (Mikolas et al., 2019), and in the right subiculum in those with MDD (Kraus et al., 2019). No studies assessed recent stressful life events or social support. Most studies assessed differences between a clinical population and healthy controls. However, six studies (Brown et al., 2019; Burhanoglu et al., 2021; Choi et al., 2017; Lim et al., 2012; Tannous et al., 2020; Travis et al., 2016) explored associations between symptomology and subfield volumes in MDD patients only. One study found no association between anxiety symptomology in those with panic disorder. Additionally, five studies (Averill et al., 2017; Chalavi et al., 2015; Hayes et al., 2017; Postel et al., 2021; Weis et al., 2021) studied symptomology in trauma survivors. Only one study (2%) assessed symptomology in community-dwelling adults (Szymkowicz et al., 2017), with no association found between subfield volume and depressive symptomology.

3.2 | Descriptive results from the Medea-7T study

Of the 333 participants in the current study, 30% were female with an average age of 68 years (Table 2). Seventeen percent experienced elevated symptoms of depression, 15% had elevated symptoms of anxiety, 24% experienced any kind of childhood maltreatment, 51% had experienced a recent stressful life event, and 24% had low social support. All subfields were significantly correlated with one another (Figure S1). Chi-square tests between each psychosocial factor showed significant associations between all psychosocial factors as well (Data S2).

3.3 | Depression and anxiety

Regarding depressive and anxiety symptomology, no significant associations were found for total hippocampal volume or within a specific subfield. However, a trend of lower volume in the total hippocampus was seen in those with depressive symptoms, and a trend of greater volume in the total hippocampus was seen in those with anxiety symptoms. Further, these trends were also seen in specific subfields. Lower volumes in the CA1 were observed in those with depressive symptomology, and higher volumes in the almost all subfields but the hippocampal tail were seen in those with anxiety symptoms (Figure 2 and Tables 3, S2, and S3).

3.4 | Any type of childhood maltreatment

For those who experienced any childhood maltreatment, a trend of lower volumes was seen in the total hippocampus and in almost all subfields but the CA3 (Figure 2 and Tables 3 and S2).

3.5 | Recent stressful event

For those who experienced a recent stressful event, a trend of greater volumes in the total hippocampus and all subfields was observed, but it did not reach statistical significance (Figure 2 and Tables 3 and S2).

3.6 | Social support

There were no associations with moderate versus low social support or high versus low social support with the total hippocampus. However,

TABLE 2 Baseline characteristics ($n = 333$)

	Mean ± SD or *n* (%)	% missing
Demographics		
Age, mean ± SD, years	68 ± 9	0
Sex, female, *n* (%)	101 (30%)	0
College/university education, *n* (%)	129 (39%)	1
Psychosocial factors		
Elevated levels of depressive symptoms, *n* (%)	55 (17%)	0
Elevated levels of anxiety symptoms, n (%)	51 (15%)	2
Any childhood maltreatment, n (%)	80 (24%)	3
Any emotional abuse	55 (17%)	3
Any physical abuse	32 (10%)	3
Any psychological abuse	44 (13%)	3
Any sexual abuse	34 (10%)	3
One or more recent life events, n (%)	171 (51%)	2
Social support, *n* (%)		4
Low social support	80 (24%)	4
Moderate social support	76 (23%)	4
High social support	177 (53%)	4
Brain volumes		
Intracranial volume, cm^3, mean ± SD	1511 ± 144	4
Entorhinal cortex, mm^3, mean ± SD	840 ± 166	13
Subiculum, mm^3, mean ± SD	1171 ± 177	13
Cornu ammonis 1, mm^3, mean ± SD	2986 ± 353	13
Cornu ammonis 2, mm^3, mean ± SD	120 ± 21	13
Cornu ammonis 3, mm^3, mean ± SD	198 ± 47	13
Dentate gyrus, mm^3, mean ± SD	1591 ± 224	13
Hippocampal tail, mm^3, mean ± SD	291 ± 67	13
Total hippocampus, mm^3, mean ± SD	6353 ± 730	13

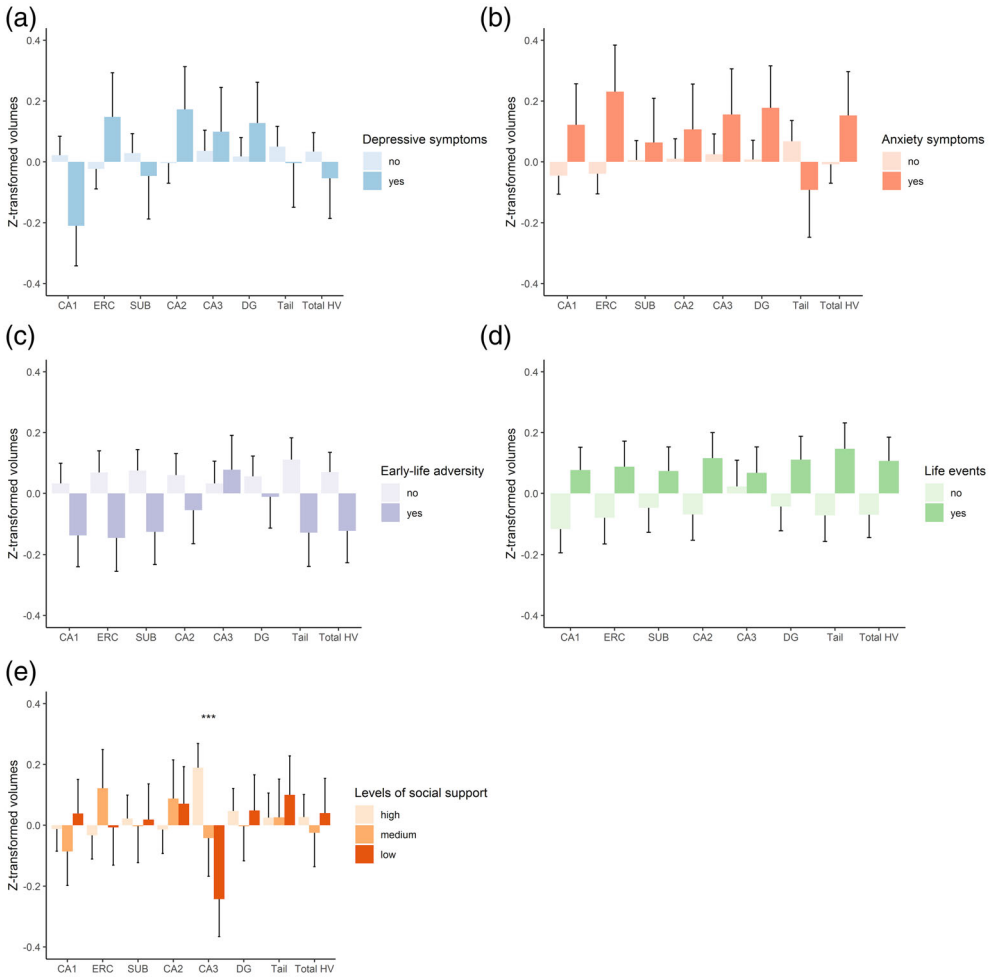

FIGURE 2 Age-, sex-, and intracranial volume-adjusted means (z-transformed) for each hippocampal subfield and total hippocampal volume per psychosocial factor. One-sided standard error bars are shown. *p* values <.05 are indicated with two asterisks (**), and *p* values <.001 are indicated with three asterisks (***). CA, Cornu ammonis; DG, dentage gyrus; ERC, entorhinal cortex, HV, hippocampal volume; SUB, subiculum.

lower volumes were seen in the CA3 in those with low social support compared to those with high social support (B per SD $= -0.43$; 95% CI: -0.72; -0.15, $p = .003$) (Figure 2 and Tables 3 and S2).

3.7 | Sensitivity analyses

When we explored specific types of childhood maltreatment, no significant associations were found with hippocampal (subfield) volume and any type of childhood maltreatment (Table 3 and Figure S2). There were trends of higher hippocampal (subfield) volumes in those who reported physical abuse and lower (subfield) volumes in those who reported sexual abuse. Additionally, a trend was also observed in those who reported sexual abuse and higher volumes in the CA3 (Table 3 and Figure S2). However, the observations within type of adversity should be interpreted with caution due to small sample size.

Due to differences in timing of the social support and childhood maltreatment questionnaires in the SMART-MR cohort as well as differences in 1.5T or 3T used for ICV segmentation between cohorts, analyses were repeated in a sensitivity analysis stratifying by cohort. Similar results were found for all subfields and total hippocampus in all three cohorts.

Sensitivity analyses on continuous psychosocial variables (i.e., BAI sum score, sum score of the recent stressful events questionnaire, and sum score of the social support questionnaire) were in line with the dichotomous results.

Sensitivity analyses when using a cut-off of 10 or higher on the PHQ-9 resulted in similar results for both hippocampal subfield volume as well as total hippocampal volume compared with using the cut-off of 6 or higher. A stronger association was found for total hippocampal volume and high depressive symptomology; however, it was still not significant.

When putting all psychosocial factors into a joint model, an association was found in the CA1 for depressive symptoms ($B = -0.34$, 95% CI: -0.65; -0.03, $p = .03$). The negative association of low versus high social support remained with the CA3 ($B = -0.44$, 95% CI: -0.73; -0.16, $p = .003$) when controlling for all other psychosocial factors (Table S3).

Lastly, when performing a complete case analysis, all associations found in the imputed analysis remained (Table S4).

4 | DISCUSSION

In our review, we found that most studies found lower volumes in association with the presence of a psychosocial factor, specifically depression, anxiety, and childhood maltreatment. Regarding

TABLE 3 Associations of each psychosocial factor on standardized volumes of each hippocampal subfield

	CA 1	ERC	SUB	CA 2	CA 3	DG	Tail	Total HV
	Estimate (95% CI), Cohen's *d*	Estimate (95% CI), Cohen's *d*	Estimate (95% CI), Cohen's *d*	Estimate (95% CI), Cohen's *d*	Estimate (95% CI), Cohen's *d*	Estimate (95% CI), Cohen's *d*	Estimate (95% CI), Cohen's *d*	Estimate (95% CI), Cohen's *d*
Depressive symptoms	−0.23 [−0.52; 0.05]	0.17 [−0.14; 0.48]	−0.07 [−0.38; 0.23]	0.18 [−0.13; 0.48]	0.06 [−0.25; 0.37]	0.11 [−0.18; 0.40]	−0.05 [−0.37; 0.26]	−0.09 [−0.37; 0.19]
	−0.23	*0.16*	*−0.07*	*0.16*	*0.06*	*0.11*	*−0.05*	*−0.09*
Anxiety symptoms	0.17 [−0.12; 0.46]	0.27 [−0.06; 0.60]	0.06 [−0.25; 0.37]	0.10 [−0.22; 0.42]	0.13 [−0.19; 0.45]	0.17 [−0.13; 0.47]	−0.16 [−0.50; 0.18]	0.16 [−0.15; 0.47]
	0.17	*0.24*	*0.05*	*0.09*	*0.12*	*0.16*	*−0.14*	*0.16*
Childhood maltreatment	−0.17 [−0.41; 0.07]	−0.21 [−0.47; 0.04]	−0.20 [−0.45; 0.05]	−0.11 [−0.37; 0.14]	0.04 [−0.22; 0.31]	−0.07 [−0.30; 0.17]	−0.24 [−0.50; 0.02]	−0.19 [−0.43; 0.04]
	−0.17	*−0.20*	*−0.19*	*−0.10*	*0.04*	*−0.07*	*−0.22*	*−0.19*
Emotional abuse	−0.12 [−0.41; 0.16]	−0.12 [−0.42; 0.19]	−0.05 [−0.35; 0.25]	0.00 [−0.32; 0.31]	−0.02 [−0.33; 0.30]	−0.03 [−0.31; 0.26]	−0.23 [−0.55; 0.08]	−0.10 [−0.39; 0.18]
	−0.12	*−0.11*	*−0.05*	*−0.00*	*−0.01*	*−0.02*	*−0.21*	*−0.10*
Physical abuse	0.28 [−0.10; 0.65]	−0.16 [−0.60; 0.27]	0.25 [−0.15; 0.66]	0.32 [−0.12; 0.77]	0.18 [−0.22; 0.59]	0.30 [−0.08; 0.67]	0.44 [−0.01; 0.88]	0.35 [−0.03; 0.72]
	0.27	*−0.15*	*0.24*	*0.29*	*0.16*	*0.29*	*0.39*	*0.33*
Psychological abuse	−0.15 [−0.47; 0.18]	−0.06 [−0.42; 0.30]	0.01 [−0.35; 0.36]	0.18 [−0.18; 0.54]	0.01 [−0.35; 0.36]	−0.13 [−0.46; 0.20]	0.09 [−0.28; 0.46]	−0.10 [−0.43; 0.24]
	−0.14	*−0.06*	*0.01*	*0.16*	*0.01*	*−0.12*	*0.08*	*−0.09*
Sexual abuse	−0.23 [−0.59; 0.12]	−0.12 [−0.53; 0.29]	−0.27 [−0.65; 0.10]	−0.21 [−0.63; 0.20]	0.37 [−0.04; 0.79]	−0.11 [−0.47; 0.25]	−0.38 [−0.77; 0.00]	−0.23 [−0.58; 0.12]
	−0.23	*−0.11*	*−0.26*	*−0.19*	*0.33*	*−0.11*	*−0.35*	*−0.22*
Recent life events	0.19 [−0.01; 0.40]	0.17 [−0.07; 0.40]	0.12 [−0.09; 0.33]	0.18 [−0.05; 0.42]	0.04 [−0.18; 0.27]	0.15 [−0.06; 0.36]	0.22 [−0.02; 0.45]	0.18 [−0.03; 0.38]
	0.20	*0.15*	*0.12*	*0.17*	*0.04*	*0.15*	*0.20*	*0.18*
Moderate vs. high social support	−0.07 [−0.33; 0.18]	0.15 [−0.14; 0.45]	−0.02 [−0.30; 0.25]	0.10 [−0.19; 0.40]	−0.23 [−0.52; 0.06]	−0.05 [−0.31; 0.21]	0.00 [−0.29; 0.29]	−0.05 [−0.31; 0.20]
	−0.08	*0.15*	*−0.02*	*0.10*	*−0.22*	*−0.05*	*0.00*	*−0.05*
Low vs. high social support	0.05 [−0.21; 0.31]	0.03 [−0.26; 0.31]	0.00 [−0.27; 0.27]	0.09 [−0.20; 0.37]	**−0.43 [−0.72; −0.15]**	0.00 [−0.27; 0.27]	0.07 [−0.22; 0.37]	0.01 [−0.25; 0.27]
	0.05	*0.02*	*−0.00*	*0.08*	***−0.40***	*0.00*	*0.07*	*0.01*

Note: Generalized linear models, adjusting for age, sex, and intracranial volume.
Abbreviations: CA, Cornu Ammonis; ERC, entorhinal cortex; SUB, subiculum; DG, dentate gyrus; HV, hippocampal volume.

hippocampal subfields, the most affected regions were the CA3 and DG. However, some studies found no association or increased association. No found studies assessed recent stressful life events or social support. This highlighted a gap in the literature assessing social support as well as differences in timing of exposure (early-life vs. late-life) in adults. In our original study using 7T brain MRI, specific psychosocial factors were associated with total hippocampal (subfield) volume. There was no association between specific hippocampal (subfield) volumes and depression or anxiety. There was a trend towards lower hippocampal (subfield) volumes in those reporting childhood maltreatment and a trend towards higher hippocampal volumes in those who experienced recent stressful life events. Psychosocial factors were generally not associated with volumetric differences within hippocampal subfields, except for low social support which was associated with lower volumes in the CA3 compared with high social support.

No association between hippocampal (subfield) volumes were found for depression or anxiety. These null findings are in line with a previous study observing null effects for depressive symptomology (Binnewies et al., 2021). However, in those with MDD diagnosis, a recent meta-analysis has highlighted lower global hippocampal volume (Santos et al., 2018). Possibly, subclinical depression may not be severe enough for hippocampal atrophy. This is in line with our sensitivity analysis on a stricter cut-off on the PHQ-9 (i.e., 10 or higher), which found a stronger association with lower total hippocampal volume and high depressive symptomology compared with using a lower

cut-off of six. Further, no association was found for anxiety symptomology and total hippocampal volume, which is in line with other studies as well (Binnewies et al., 2021; Dannlowski et al., 2012; Levita et al., 2014). Although, there was a trend towards higher hippocampal volume in those with anxiety symptoms, which is in agreement with a previous study that also found a nominal positive association (Womersley et al., 2020). To note, this trend was driven by the entorhinal cortex, which is the major input and output structure to the hippocampus.

The current study found a trend towards a difference in early- versus late-life stressful events and total hippocampal volume. A trend towards lower hippocampal volume was observed in those who reported childhood maltreatment. This is in line with previous literature on clinical PTSD (Zhang et al., 2021), as well as on previous childhood maltreatment (Dannlowski et al., 2012). Further, this highlights a possible role of programming effects. Epigenetic programming (i.e., when an environmental stimulus that occurs during development has an impact on DNA methylation and other epigenetic markers) has been hypothesized to explain the link between childhood maltreatment and risk for adult pathophysiology (McKinney, 2017). Programming effects can also occur via the HPA axis (Matthews & McGowan, 2019), as studies have shown that stress in early life can impair the neuroendocrine homeostasis in the HPA axis in the long-term (de Bellis et al., 1994). Please see McGowan (2013) for a review on early-life stress and programming effects. In contrast, a trend towards higher volumes in the hippocampus were seen in those who experienced a recent stressful event, which is in line with a previous study (Zannas et al., 2013). However, other studies found a negative association (Bootsman et al., 2016) or no association (Bootsman et al., 2016; Gerritsen, Kalpouzos, et al., 2015). Discrepancy in the literature could be due to the severity of the life event or timing of the life event, as one study (Bootsman et al., 2016) did not find an association with midlife events or total life events, only with increasing severity. Some studies have postulated that stress exposure may have a biphasic effect on the hippocampus, with acute increases in volume due to metabolic activity followed by later atrophy (Machado-de-Sousa et al., 2014). These studies highlight a possible timing effect, as well as a possible difference in the severity of stress exposure, with hippocampal volume and should be investigated further.

Previous literature, specifically in animal models, has shown that the hippocampus is heterogeneous regarding stress sensitivity. The CA3 and DG show specific sensitivity to stress through dendrite remodeling and neurogenesis inhibition as a response to chronic stress. The current study highlights that social support may play a protective role of these sensitive regions as higher volumes were found in the CA3 in association with high social support, even when correcting for other psychosocial factors. This finding in the CA3 could reflect possible protective effects of social support on episodic memory (Kelly et al., 2017), which the CA3 is responsible for. While little research has been conducted on specific subfield volume, some studies have explored total hippocampal volume with social support. Previous studies have been mixed, with some studies reporting no association (Förster et al., 2021) and one study also finding a positive association with total volume (Kim et al., 2020). However, no other differences in subfields were found for other psychosocial factors. This is in line with a previous study looking at symptomology rather than specific clinical diagnosis, with finding no differences associated with depressive symptomology in community-dwelling adults (Szymkowicz et al., 2017). This could highlight that hippocampal subfields are not sensitive enough to differential volumetric associations when looking at symptomology only. However, volumetric differences could be visualized with trends based on psychosocial factor.

To assess differences regarding type of childhood maltreatment, we performed a sensitivity analysis based on maltreatment type. Trends regarding specific differences were found in those who experienced physical abuse as well as in those who experienced sexual abuse. A previous meta-analysis (Baumeister et al., 2016) on childhood maltreatment and adulthood inflammation also found significant increases in inflammation specifically in physical and sexual abuse. A trend towards higher volumes were found in almost all hippocampal subfields in those who reported physical abuse. This trend of increased volume may reflect signatures of resiliency in later life. A trend towards lower volumes in the total hippocampus is in line with previous research on atrophy associated with childhood sexual abuse (Andersen et al., 2008). Surprisingly, we also observed a trend between reporting sexual abuse and higher CA3 volume. A previous study found increased volumes in those reporting sexual abuse, specifically in the HATA (Ahmed-Leitao et al., 2019). Reporting sexual abuse may lead to a resiliency later in life in subfields related to emotional processing, reflected by increased volumes in these specific subfields. These types of maltreatment may have specific biological consequences and require further investigation.

Strengths of the current study include using high-field 7T MRI, as well as using the validated and readily available ASHS software for segmentation of subfields in the hippocampus. Previous studies have mostly used 1.5T or 3T MRI (Table 1), which may make differentiation between subfields more difficult for assessment and more prone to noise. Missing data was handled using multiple imputation to avoid loss of power, and multivariate models were used to account for correlation between the subfields and to reduce the possibility for false positives when performing multiple tests. The current study consisted of 333 participants, larger than previous studies assessing psychosocial factors and subfield volumes (Table 1). However, our standard errors were large, with many volumes showing trends towards significance. Future studies with larger sample sizes should be performed to increase power and validate findings within subfields.

A limitation is that the current study is cross-sectional; thus, we were unable to look longitudinally on the effect of psychosocial factors on hippocampal subfield volumes. Future studies should consider longitudinal assessment of psychosocial factors and hippocampal volumes during the aging process to explore their effect in detail on neurodegeneration. Additionally, we only correct for a minimal number of confounders (i.e., age, sex, and ICV) for consistency due to studying multiple psychosocial factors that have varying confounders. However, we did perform a sensitivity analysis of a joint model using all psychosocial factors to assess their impact on one another. There

could be residual confounding in the current study and future studies should include possible confounders per psychosocial factors for validation. Most participants originated from the SMART-MR study, where all individuals have a history of vascular disease; therefore, these results may not be generalizable to other populations. It is also critical to note that these participants mostly came from a White, Western background. Studies have shown that marginally underrepresented populations also experience a disproportionately larger amount of maltreatment (Lanier et al., 2014). Future studies need to be done to assess the effect of psychosocial factors on hippocampal subfields in these populations. Further, there were some differences between cohorts regarding study protocol. Specifically, social support and childhood maltreatment were assessed at an earlier time point in the SMART-MR cohort, as well as differences in MRI strength between studies for ICV segmentation, which could have affected the current findings. However, sensitivity analyses when stratifying by cohort led to similar results. Lastly, our finding in the CA3 subfield should be interpreted with caution, as the CA3 is one of the smallest subfields within the hippocampus and therefore prone to measurement error, possibly including portions of the CA2, CA3, or DG. More studies assessing social support and hippocampal subfield volume are warranted for validation of our finding on CA3 volume.

Conclusively, the current study highlights that hippocampal (subfield) volumes may differ based on the psychosocial factor. Consistency between subfield volumes or differential effects also may depend on the psychosocial factor. As the hippocampus is involved in both emotional and memory processing, understanding the effects of psychosocial factors on hippocampal decline is crucial in the prevention of neurodegenerative diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

For use of anonymized data, a reasonable request has to be made in writing to the study group and the third party has to sign a confidentiality agreement.

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