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Structural Neuroimaging of Hippocampus and Amygdala Subregions

in Post-Traumatic Stress Disorder (PTSD): A Scoping Review

Short Title: Hippocampus and Amygdala Subregions in PTSD

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Abstract

Numerous studies have explored the relationship between posttraumatic stress disorder (PTSD) and the hippocampus and the amygdala, as both regions are implicated in the disorder's pathogenesis and pathophysiology. Nevertheless, those key limbic regions consist of functionally and cytoarchitecturally distinct substructures that may play a different role in the etiology of PTSD. Spurred by the availability of automatic segmentation software, structural neuroimaging studies of human hippocampal and amygdala subregions have proliferated in recent years. Here, we present a pre-registered scoping review of the existing structural neuroimaging studies of the hippocampus and amygdala subregions in adults diagnosed with PTSD. A total of n=3513 studies assessing subregions volumes were identified, n=1689 of which were screened, and n=21 studies were eligible for this review (total n=2876 individuals). Most studies examined hippocampal subregions and reported decreased CA1, CA3, dentate gyrus and subiculum volumes in PTSD. Fewer studies investigated amygdala subregions and reported altered lateral, basal, and central nuclei volumes in PTSD. This review further highlights the conceptual and methodological limitations of the current literature and identifies future directions to better understand the distinct roles of hippocampal and amygdalar subregions in post-traumatic psychopathology.

Introduction

A substantial body of neuroimaging literature investigated the relationship between posttraumatic stress disorder (PTSD) and the morphology of the hippocampus and the amygdala[1], [2]. These limbic regions have prominent roles in neurobiological models of PTSD, including fear learning, threat and salience detection, emotion regulation, and contextual processing[3]. Importantly, the hippocampus and the amygdala are not homogeneous structures but rather consist of cytoarchitecturally and functionally distinct subregions (also referred to as 'hippocampal subfields' and 'amygdala nuclei'). In recent years, new automated tools and protocols for subregion segmentation were introduced into human neuroimaging, allowing a more detailed examination of the different parts of the hippocampus and amygdala[4]–[7]. These methodological advancements have opened new avenues for research into the unique roles that different subregions might play in the etiology of post-traumatic psychopathology.

The hippocampal complex is critical for encoding emotional memories and modulating appropriate emotional responses to fearful stimuli, making it a key region in the investigation of post-traumatic psychopathology[8], [9]. While changes in hippocampal activity in PTSD are not consistent[10], smaller hippocampal volume is the most consistent structural abnormality in PTSD[11], [12]. However, examining the hippocampus as a whole ignores its heterogeneity[13] and might mask abnormalities in specific subregions that are differently affected in PTSD[14]. The hippocampus is a complex and highly specialized structure, composed of multiple subregions with distinct cellular layers, circuitry, and functions[15]. Based on histology, the hippocampus proper (cornu ammonis, CA) is divided into two main parts, CA1 and CA3 (often combined with CA2), which are composed of pyramidal neurons organized in a laminar fashion. The dentate gyrus (DG), located at the border of the hippocampus proper and the entorhinal cortex, is densely packed with granule cells. The DG also includes the polymorphic region, referred to as the CA4. The subiculum, located between the CA1 and entorhinal cortex, is the main output region of the hippocampus.

Animal models of PTSD suggest that the hippocampus mediates the stress response and release of glucocorticoids from the hypothalamic–pituitary–adrenal (HPA) axis[16], and that chronic activation of the HPA axis due to stress may in turn cause hippocampal volume loss[17]. Animal research further indicates that discrete hippocampal subregions could be relevant to the neurobiology of fear, anxiety and PTSD. For instance, Snyder and colleagues (2019)[18] reported that mice without adult neurogenesis were more susceptible to anxio-depressive-like behavior following acute stress, suggesting that new neurons in the hippocampal DG are critical for the regulation of the HPA axis response to stress[18]. Another study examining a rat model of PTSD point to the ventral CA1 subregion of the hippocampus as a potential key mediator of stress-induced anxiety-like behavior[19]. In contrast to animal studies of PTSD, human neuroimaging research has primarily focused on the structure and function of the whole hippocampus until recent years.

The amygdala is another brain structure strongly implicated in PTSD pathophysiology[20], with over 30 years of research in the context of threat learning and extinction[21], [22]. Specifically, it is critically involved in fear response, conditioning, and generalization[23]–[26], and facilitates the response to stressful traumatic events[8]. Patients diagnosed with PTSD typically show hyperactive amygdala in response to affective and trauma-related stimuli, with this activation correlated with symptom severity[27], [28]. Evidence of altered whole amygdala volume in PTSD is equivocal, with findings of no difference, smaller or larger amygdala volumes in patients relative to controls[1], [2], [11], [29]. Like the hippocampus, rather than being a unitary structure, the amygdala is formed from a collection of interconnected subregions (nuclei) that relay signals from multiple brain areas (i.e., cortical and subcortical subregions)[30]. These nuclei can be distinguished on the basis of cytoarchitectonics, histochemistry and the connections they make[31], [32]. Traditionally, the amygdala can be divided into two broad complexes, the centrocorticomedial (CMA) division and the basolateral (BLA) division[33]. The CMA includes the central, medial and cortical amygdala nuclei, whereas

the BLA includes the basal, accessory basal and lateral nuclei[34]–[36]. The CMA is densely interconnected with the striatum, brainstem and the hypothalamus, while the BLA is extensively interconnected with sensory and prefrontal cortical areas, thalamus and the hippocampus[37], [38].

Animal studies showed changes in amygdala morphology in relation to chronic stress, or unique features of structural plasticity in the amygdala (e.g., traumatic stress leads to trophic changes and synaptogenesis in the amygdala)[10], [39]. After decades of studying animal models of PTSD, it seems that specific amygdala subnuclei are responsible for alterations in certain fear-, anxiety-, and stress-related behaviors. The BLA appears to be necessary for the formation and/or expression of associative fear memories, with its lateral nucleus serving as a convergence site for sensory and aversive information that is relayed to the central nucleus to drive fear-related behaviors[40]–[42]. Indeed, smaller BLA volumes were associated with increased levels of fear conditioning and excessive glucocorticoid stress response[43], [44]. While much progress has been made using animal models of PTSD to understand the involvement of amygdala subregions in fear conditioning and extinction, the gained knowledge did not yet translate to better knowledge or treatments for PTSD patients[45].

Advances in human neuroimaging techniques, including high-resolution magnetic resonance imaging (MRI) and continuously developing analysis software, enable non-invasive in-vivo visualization and quantitative macro-anatomical characterization, based on differences in tissue properties of specific brain structures[46]. However, hippocampal and amygdala segmentation into subregions from MR images is methodologically challenging, given their small size, anatomical complexity and cellular morphology[47]. In response, studies that combined cyto- and chemo-architectural analyses with macroscopic landmarks were able to better separate different hippocampal and amygdala subregions in humans using MRI images[48]. Moreover, recent advances in gradient mapping techniques and in-vivo parcellation allowed characterization of both medial-to-lateral and anterior-to-posterior hippocampal axes, that may

allow better understanding of the human hippocampal organization and function[49]. In line with the growing emphasis on obtaining larger sample sizes to achieve sufficient statistical power[50], manual delineation of subfields, a process that requires significant time and expertise, is becoming less practical. While manual segmentation has its advantages, it always involves some degree of subjectivity, and such variability poses significant challenges for replication[51], [52]. Overcoming these barriers, several automated subregion segmentation protocols for the amygdala and hippocampus were developed in recent years, providing high-resolution, standardized and relatively reliable segmentation[4]–[7], [53], [54].

Among the available automated tools, FreeSurfer[55] (surfer.nmr.mgh.harvard.edu/) is one of the most widely used. FreeSurfer first introduced hippocampal subfields segmentation in version 5.3 (2009)[7], and added the segmentation of amygdalar nuclei to it in version 6.0 (2017)[5]. Importantly, the early version (FreeSurfer 5.3) of hippocampal segmentation has been criticized for underestimating CA1 volumes and overestimating the subiculum in the hippocampal head (where the boundary between the two subfields is more difficult to delineate)[56], [57]. Since then, FreeSurfer keeps developing and improving its segmentation modules, with the recent version at the at the time of writing is 7.3.2 (Aug, 2022), allowing cross-sectional and longitudinal segmentation of the hippocampus, amygdala, thalamus and brainstem (surfer.nmr.mgh.harvard.edu/fswiki/SubregionSegmentation). The recent segmentation modules of FreeSurfer demonstrate good reliability for larger amygdalar and hippocampal subregions, even at multisite MRI studies[58].

Given the improvements in recent automatic segmentation algorithms and the growing number of studies focusing on subregions of the hippocampus and amygdala in PTSD, a review of the existing empirical research is not only timely, but also imperative. As current MRI literature on subregion volumes in PTSD is still emerging and constrained, there is a need to map out key concepts, identify knowledge gaps, and highlight potential future directions, rather than synthesize the results quantitatively or draw definitive conclusions. Therefore, we

employed a scoping review methodology[59], rather than a systematic review or meta-analysis[60], to evaluate existing MRI studies of hippocampus and amygdala subregions morphology (i.e., volume and shape) in adults diagnosed with PTSD. While others reviewed neuroimaging studies of hippocampal subfields (but not amygdala nuclei) in schizophrenia and bipolar disorder[46] or in relation to psychosocial factors[14], this is the first one to review the structure of both hippocampal and amygdala subregions in PTSD. We aimed to synthesize findings from a variety of study designs and populations, to detect consistent and contradicting results, and to determine whether a future systematic review is needed and/or feasible. Finally, we discuss important conceptual and methodological limitations and suggest future directions in neuroimaging of hippocampal and amygdala subregions in post-traumatic psychopathology.

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Methods

Protocol and registration. This scoping review is informed by the framework described by the Joanna Briggs Institute (JBI)[61], [62] and follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols Extension for Scoping Reviews (PRISMA-ScR) guidelines[59]. The protocol for this review was publicly pre-registered with the Open Science Framework (OSF) on March 24, 2022 (doi.org/10.17605/OSF.IO/RCG8E), prior to the begging of the actual review process.

Eligibility criteria. We included peer-reviewed studies using structural neuroimaging (MRI) of adult human subjects diagnosed with PTSD (i.e., patients) and controls (e.g., trauma-exposed and/or healthy individuals), which had at least one quantitative volumetric measure of hippocampus subfields and/or amygdala nuclei. The term 'subregions' usually refer to both the amygdala and hippocampus, while 'subfields' is usually used for hippocampus and 'nuclei' for the amygdala. Any work which included animal models, non-adult population (i.e., participants under 18 years of age), individuals with traumatic brain injury (TBI) or head injury, was excluded. Any research that was not peer-reviewed, did not have a full text, or assessed only qualitative measures of the subregions, was similarly excluded. For the full list of inclusion and exclusion criteria, see Supplementary Box S2.

Information sources and literature search. An experienced medical librarian consulted on methodology and ran a medical subject heading (MeSH) analysis of known key articles provided by the research team[63]. On March 30, 2022, a comprehensive search of multiple databases was performed: MEDLINE, EMBASE, APA PsycInfo, Cochrane CENTRAL, and Web of Science. For more details, see Supplementary Methods and Box S2.

Selection of sources of evidence, data charting and data items. Search results were pooled in *EndNote* version 20 [www.endnote.com][64] and duplicates were removed[65]. This set was then uploaded to *Covidence* platform [www.covidence.org][66], in which additional duplicates were identified and removed. The review process included three stages: (1) titles and

abstracts screening, (2) full-texts screening and (3) data extraction (for full details, see Supplementary Materials and Figure 2).

Synthesis of Results. Upon a preliminary abstraction, the research team decided to group together studies that inspected the volumes of hippocampal subregions, amygdala subregions, or both (Table 1A, 1B, and 1C, respectively). The rationale was to group the most similar types of studies to ensure their differences could be adequately compared. The reviewers then extracted the relevant data for each the article: first author and year of publication, country of study site, sample size, gender distribution, mean age, study groups, research design, trauma type, PTSD measure, MRI field strength, subfield segmentation technique, the examined subregions, and the main findings regarding the associations between subregions' morphology and PTSD diagnosis and severity (see Table 1).

The main findings of the different studies were summarized separately for studies of hippocampal subfields (n=19, Table 1A and 1C)[12], [67]–[83] and those of amygdala nuclei (n=5, Table 1B and 1C)[12], [73], [83]–[85]. The main challenge of the results synthesis in this review was the large variability between studies regarding the number and specific subregions that were analyzed (see Table 1). A secondary challenge was the subregions' parcellation, as studies differed substantially on which and how the subregions were defined, as well as whether they were studied bilaterally or unilaterally. To overcome this challenge, we grouped subregions based on: (1) well-established literature of their anatomy and function[15], [86], [87], (2) their absolute size, as larger amygdalar and hippocampal structures demonstrated better test-retest reliability across different MRI sites and vendors[58]. These subregions are described in the Supplementary Methods and illustrated in Figure 1.

Results

Overview of Studies. A final number of n=21 studies, published between 2010 and 2022, fulfilled the inclusion/eligibility criteria were included in this review[12], [67]–[85] (for study selection, see Supplementary Results). Overall, sixteen studies (76%) tested only hippocampal subfields (Table 1A)[67]–[72], [74]–[82], two (10%) tested only amygdala nuclei (Table 1B)[84], [85], and three (14%) tested both hippocampal and amygdala subregions (Table 1C)[12], [73], [83]. About half of the studies were conducted in the United States (n=11, 52%), while the others were conducted in China (n=4, 19%), Netherlands (n=2, 10%), Israel, France, Norway and South Africa (n=1, 5%, each). Sample sizes varied greatly, from the smallest study including 36 individuals (17 diagnosed with PTSD)[80] to the largest including 355 subjects (149 diagnosed with PTSD)[84]. The average sample size was 137 individuals (SD=91), with half of the studies having a sample size above 100 participants (Median=100). Gender distribution also varied between studies, from those which included only females (n=1, 5%)[70] to those which included only (combat-exposed) males (n=3, 14%)[76], [79], [80]. Overall, there was a balanced gender distribution across all studies (median of 54% females). Participants' average age ranged from 21 to 57 years, with a mean age of 37±9 years. For detailed overview of the studies included, please see Supplementary Results.

Hippocampal Subregions in PTSD. Hippocampal subregions were examined in n=19 studies and across N=2422 participants. The **CA1** was examined in 84% of studies (i.e., n=16 out of 19) and 89% of participants (i.e., N=2167 out of 2422). The majority of these studies (n=9 out of 16, 66%) found no association between the CA1 morphology and PTSD diagnosis or symptom severity (N=1170 participants). The remaining seven studies (44%) found CA1 to be significantly associated with PTSD[12], [70], [71], [76], [77], [79], [88]. Of these, five studies (N=635 participants) reported smaller CA1 volumes in PTSD patients (compared to TEC or HC) or in individuals who developed non-remitting PTSD (compared to those who remitted)[12], [70], [71], [79], [88]. Two of the five studies were referring to the bilateral CA1, two studies to the right

CA1, and one to the left CA1. Additionally, a genetic study reported significant interactions between genetic variants and childhood trauma/lifetime PTSD within the CA1 subregion[77]. A neurofeedback study found an increased volume in left CA1 head in the experimental group, and decreased volume in the same region in the control group[76].

The **CA3** was investigated in 89% of the studies (n=17) and in 96% of participants (N=2332). About half (n=8 studies, 47%) found no significant association between CA3 volume and PTSD (N=1243 individuals). The others (n=9, 53%) report lower bilateral CA3 volume in PTSD patients (compared to controls) and/or linked it to more severe symptoms (N=1089 individuals)[68], [70], [71], [74], [79], [80], [82], [83], [88]. Lower CA3 volume in PTSD compared to TEC was found in four studies[71], [79], [80], [88], while four others observed similar volumes in both groups[68], [74], [82], [83] (and one did not have a TEC group[70]). Interestingly, two studies found an association between CA3 volume and PTSD severity only among the PTSD group, and not across all subjects[68], [88].

The **dentate gyrus (DG)** was examined in 84% of the studies (n=16) and in 89% of participants (N=2167). Half of them (n=8, 50%), including N=1252 individuals, report no significant associations between DG volume and PTSD. The other half (n=8, 50%) found lower DG volume in PTSD patients (compared to controls) and/or associated with more severe symptoms across N=915 participants[70], [72]–[74], [79], [80], [83], [88]. This reduced volume was observed bilaterally in most studies (n=6), with two reporting significant results for one, but not the other, hemisphere[70], [73]. Specifically, a longitudinal study of police recruits observed that smaller left DG at baseline was associated with more severe PTSD symptoms at 16-months follow-up[73]. A recent work which combined the CA2, CA3 and DG into a single subregion, found it to be specifically associated with more avoidance and hyperarousal PTSD symptoms[88].

The **subiculum** was examined in 79% of the studies (n=15) and 76% of participants (N=1848). Seven of these studies (47%) found similar volumes of the subiculum between PTSD

patients and controls (N=807 individuals). The others (n=8, 53%) report a significant link between subiculum volume and PTSD (N=1041 individuals)[12], [67], [70], [74], [77], [79], [83], [88]. Most of the evidence (n=5) support smaller subiculum volumes in PTSD patients, compared to TEC and/or HC. However, a study of earthquake survivors which compared three groups (PTSD, TEC, HC) observed larger right pre-subiculum in PTSD patients than in TC (but smaller than in HC)[83]. A longitudinal study of recent trauma survivors observed smaller bilateral subiculum volume in individuals who still met PTSD diagnosis at 14-months post-trauma (i.e., non-Remission), compared to those who recovered from initial symptoms (i.e., Remission)[12]. While four studies reported an association with volumes of the bilateral subiculum, five others found this association with volumes of the unilateral subiculum (three studies in the left hemisphere and two in the right one).

Finally, the two (out of 19) studies which performed additional shape analysis of hippocampal subfields did not find significant differences between PTSD and controls in a total sample of 343 individuals[70], [71]. For results of additional hippocampal subregions, see Supplementary Results and Table 1.

Amygdala Subregions in PTSD. The main amygdalar subnuclei - the lateral, basal, and central amygdala - were examined in all five studies and across N=967 participants. The **lateral amygdala (LaA)** was not associated with PTSD in three (60%) of those studies and in N=522 individuals[12], [73], [83]. Two investigations reported altered LaA volumes in PTSD (N=454 participants)[84], [85]. Specifically, smaller bilateral LaA volume was observed in PTSD patients compared to TEC[84], and smaller right LaA was associated with less PTSD symptom reduction (from 4-5 to 24-36 months post-trauma)[85].

The **basal amygdala (BaA)** volume was correlated with PTSD in three (60%) of the studies (N=521 individuals)[73], [83], [85]. Of these, two research papers which examined survivors of single traumatic events (i.e., earthquake and terror attack) reported smaller right BaA volumes in PTSD (compared to HC)[83] and in correlation with more severe symptoms[85].

On the contrary, a longitudinal work tracking police recruits found that greater amount of trauma exposure was associated with increased left BaA volume (during a 16-month time period)[73]. Two other studies (40%) found no association between BaA morphology and PTSD diagnosis or severity in a total of N=455 participants[12], [84].

The **central amygdala (CeA)** subregion was linked to PTSD in three (60%) out of the five studies (N=655 participants)[77], [83], [85], with mixed results. While one research group reported larger left CeA in PTSD compared to TEC[77], a second one found similar bilateral CeA volumes in PTSD and TEC, both of them significantly smaller than HC[83]. A third study concluded that smaller right CeA volumes are related to more severe PTSD symptoms[85]. The two other studies (40%) found similar volumes of the BaA in PTSD patients and controls in a total of N=321 individuals[12], [73].

Finally, the single paper testing amygdala subregions shape analysis found that both radial distance (in the anterior amygdala) and Jacobian determinant (in the posterior amygdala) were lower in N=149 PTSD patients (compared to N=206 TEC)[84]. For results of additional amygdalar subregions, see Supplementary Results and Table 1.

Discussion

   This scoping review aimed to summarize findings from existing structural neuroimaging studies of hippocampal subfields and/or amygdala nuclei in adults diagnosed with PTSD. Following PRISMA-ScR guidelines[59], we identified 21 structural MRI studies examining the morphology of these limbic subregions across 2876 individuals (n=1354 PTSD patients and 1522 controls). While a significant body of literature documents structural alterations of hippocampal subregions in PTSD (n=19 studies), there is a relative dearth of research examining amygdalar subregions volumes in this disorder (n=5 studies). Currently, a systematic review or meta-analysis of the amygdala and hippocampal subregions volumes in PTSD is premature, mainly due to the insufficient data and the lack of standardization across studies.

   While most studies of hippocampal subregions report decreased volumes in PTSD patients, the exact subregions affected are inconsistent across studies. Despite the heterogeneity in the methods and results of the reviewed studies (discussed below), we found that the **CA1**, **CA3**, **DG** and **subiculum** were most investigated subfields. Results indicated that they were significantly associated with PTSD in **44%**, **53%**, **50%** and **53%** of the studies and across **29%, 47%, 42%** and **56%** of the participants, respectively. Much less studies examined amygdala subregions in PTSD (n=5), and these report mixed findings of decreased, increased or similar volumes between PTSD patients and controls. The **lateral**, **basal** and **central nuclei** of the amygdala were examined across all five studies. Results revealed that they were significantly associated with PTSD in **40%**, **60%** and **60%** of the studies and across **47%, 53%, 67%** of the participants, respectively. There is a pressing need for more research on amygdala subregions morphology in relation to PTSD.

   Future research is needed to better understand the relation between specific hippocampal and amygdalar subregions and clinical manifestations of PTSD, and specifically the hypothesis that these subregions may be differentially associated with distinct PTSD symptom clusters. For instance, the hippocampal DG is involved in memory encoding and

retrieval, by separation of overlapping (perceptually similar) sensory inputs through pattern separation[89]. Thus, if the DG is impaired, it could lead to an inability to distinguish between different cues, which can be manifested as fear generalization in the context of PTSD[90], [91]. Within the amygdala, the basolateral nucleus plays a role in fear learning, while the centromedial nucleus is important for fear expression through its projections to the brainstem and hypothalamus[42]. Dysfunction of these nuclei might result in greater fear response, re-experiencing and hyperarousal symptoms[43], [92]. Disentangling which subregions are linked to which impaired processes in PTSD (e.g., memory, learning), may enhance our mechanistic understanding of the disorder's pathophysiology, as these subregions show structural and functional heterogeneity. If different subregions are involved in unique processes that contribute to specific behavioral manifestations, examining the structure and function of the whole hippocampus or amygdala might yield null results or bias results towards more robust processes.

Conceptual and Methodological Challenges. This review highlights several shortcomings in conceptualization and methodology of the current literature of hippocampal and amygdala subregions in PTSD. A main issue identified was the large variability across studies in which subregions were examined and how many of them, ranging from one to 28 different subregions (see results). This problem is rooted in the large variability of the subfield segmentation methods (e.g., FreeSurfer, VBM using SPM, ASHS, visual assessment; see Table 1). Even among studies using the same segmentation method (FreeSurfer), at least three different software versions (v5.1, v.6.0, v.7.1) were used. To note, FreeSurfer v5.1 was previously criticized for its low construct validity and consequently deprecated[93], [94], questioning the generalizability of findings based on this segmentation method[70], [72], [74]. With regard to visual assessment/segmentation of the subregions, while it has some clear advantages, it is time-consuming thus infeasible for large studies[95], and also requires some subjectivity thus vulnerable to error[50]. Finally, while most studies (66%) chose to analyze

subregions separately for each hemisphere, one-third (33%) analyzed bilateral volumes, further contributing to the variability in the number of examined subregions.

Another methodological choice that influenced the results was the subjective decision on how to group different subregions. For example, while most studies separated between the DG and CA3 subregions, one study[88] combined CA2, CA3, and DG into a single subregion, and two others separated the CA3 and the DG each subregions into head and body[76], [83]. Moreover, some studies divided the hippocampus only to two (e.g., anterior and posterior)[78] or three parts (e.g., anterior, posterior, and subiculum)[69]. An additional subjective decision that increased the differences in the type and number of examined subregions was the authors decision on testing specific subregions a-priori and/or testing all subregions in an exploratory post-hoc manner. To conclude, methodological differences and shortcomings might explain the contradictory and often inconsistent findings, highlighting the pressing need for standardization and methodological improvements in this field.

Several confounding factors might affect the results of the studied reviewed (and other results from structural neuroimaging of psychiatric populations). Although beyond the scope of this work, both alcohol[96], [97] and cannabis[98] are known to be hippocampal toxins and have been showed to affect hippocampal subregions differently. Alcohol dependence can induce significant and non-reversible hippocampal volume loss[99]–[101], and regular cannabis use might cause a significant decrease in amygdala's volume[102], [103]. Moreover, antidepressant medications (i.e., selective serotonin reuptake inhibitors) have been shown to increase angiogenesis and neurogenesis in the DG[104], and atypical antipsychotic medications (e.g., olanzapine and clozapine) were associated with increased hippocampal neurogenesis and cell-proliferation[105]. It is yet unclear whether antidepressants and antipsychotic medications influence amygdala subregional volumes[106], [107]. Furthermore, stressful or traumatic childhood experiences might lead to volumetric changes in hippocampal and amygdala subregions. Changes in size of both these limbic regions could be mediated through

dysregulated glucocorticoid release and increased inflammation following childhood abuse[108], [109]. Excessive glucocorticoid levels might cause decreased neurogenesis, atrophy of dendritic processes and even hippocampal neurotoxicity[110]. The hippocampus may be vulnerable to early life stress due to the high density of glucocorticoid receptors and persistent neurogenesis[111], with traumatic experiences potentially decreasing overproduction of synapses, leading to smaller volume[112], [113]. Last but not least, recent work provided evidence for postnatal neurogenesis in the human amygdala, in a similar magnitude as suggested to exist within the hippocampus[114], suggesting that amygdalar plasticity might be similar to hippocampal one. In conclusion, future neuroimaging studies of PTSD should assess (and control for, if possible) other factors that can influence neurogenesis in the hippocampus and amygdala (e.g., alcohol and cannabis use, antidepressant and antipsychotic medications, traumatic stress at childhood, pregnancy).

Beyond the methodological issues impeding the interpretation of the reported results, there are also questions concerning the underlying causes of hippocampal and amygdala subregions volume alternations in post-traumatic psychopathology[115], [116]. Most studies reviewed here were cross-sectional (81%), thus cannot disentangle predisposed from acquired volume abnormalities[117]. However, results of the four longitudinal studies to date[12], [73], [76], [81] generally suggest that volumetric alterations in the hippocampal and/or amygdala subregions reflect pre-trauma vulnerability traits, rather than acquired post-trauma consequences. It is also possible that persistent stress symptoms cause gradual subregion volume reduction over longer time periods (e.g., years instead of months). Future longitudinal studies with longer follow-up durations are needed to address this yet unresolved question.

Limitations. This review has several limitations to be acknowledged. First, due to its scoping nature, the quality of the data from the different studies was not assessed. Rather, our aim was to present a synthesized, up-to-date, overview of MRI volumetric studies of hippocampus and amygdala subregions in PTSD, to detect consistent and inconsistent findings,

and to determine the feasibility of a future systematic review. Second, due to the relatively small number of studies reviewed, and their significant variability with regard to demographic and clinical variables, we were not able to review their impact in the present review. However, we did assess those putative confounders (e.g., age, gender, trauma type, clinical measures) in each study, and report them in the results summary and in Table 1.

Future Directions. Future studies should meticulously incorporate unified parameters of segmentation protocols to encourage standardization, reproducibility and replicability[51]. To that end, using high field strengths (at least 3T), better spatial resolution (less than 1mm^3), and combining T1-weighted and T2-weighted scans would improve the data quality in terms of acquisition[4], [118]. In terms of data analysis, simultaneous segmentation of both the hippocampus and the amygdala is highly preferred to overcome the issue of their anatomical proximity (i.e., joint segmentation ensures that structures do not overlap or leave gaps in between)[5], [30]. Studies should preferably use more than one version or tool for subregion segmentation, to ensure the accuracy and generalizability of the results. In terms of study design, as traumatic events may have an enduring effect on the brain, even in the absence of symptoms[119], future work should directly compare PTSD patients to both trauma-exposed and trauma-naïve control groups. Finally, studies should present all their neuroimaging results, highlighting key ones, and not hiding subthreshold ones, to enhance interpretation, reduce biases, and improve reproducibility[120].

Notwithstanding the methodological suggestions for future research, this review also points to several conceptual recommendations. First, research should integrate knowledge about hippocampal and amygdala structure and function in PTSD, as tested in-vitro and in-vivo in animal models with implications of behavior that could be further investigated in human neuroimaging studies[46], [121], [122]. Translational insights from animal models of PTSD could contribute to clinical human neuroimaging studies, informing theory-driven hypotheses regarding specific subregions that might be associated with specific PTSD symptoms (e.g.,

hyperarousal, avoidance). Second, as alternations in these limbic subregions were reported

across a variety of psychiatric disorders, and in line with the NIMH Research Domain

Criteria[123], studies should study their structure in a transdiagnostic approach. For example,

recent work showed that hippocampal volumes vary with transdiagnostic psychopathological

dimensions, specifically increased distress and anxious arousal were associated with reduced

hippocampal CA1 and CA4/DG volumes[124]. Third, given the inconsistent results found in this

review, it is imperative to adhere to good scientific practice. That is, authors should clearly

distinguish between hypotheses established before data collection (a-priori) and those formed

after (posteriori), and to properly correct for multiple comparisons. They should also report

negative or null findings, which often go unpublished, leading other investigators into redundant

studies. A good way to promote reproducibility and transparency is the use of Registered

Reports, a form of empirical publication in which study proposals are peer reviewed and pre-

accepted before research is undertaken[125], [126]. Another recommended practice is sharing

the data and the code to increase transparency, reliability and collaboration between research

teams[127].

Several promising recent studies examined the resting-state functional connectivity of

hippocampal[128], [129] or amygdalar subregions [130], [131] in PTSD. Although beyond the

scope of this review, functional neuroimaging studies of hippocampal and amygdala subregions

in PTSD hold great potential for advancing our understanding of the disorder. Nevertheless, it is

important to recognize the limitations and challenges associated with this line of research.

Notably, investigating amygdala function and connectivity in humans is prone to imaging

artifacts due to its small volume[27], and studying even smaller subregions within the amygdala

may be particularly susceptible to such artifacts[130]. Furthermore, while functional connectivity

analysis estimates the temporal correlation between activations of brain areas, it does not

provide information on the direction of these correlations, warranting further investigation using

structural and effective connectivity measures. Despite these limitations, future research on the

interrelationships within and between hippocampal and amygdala subregions could offer valuable insights into the neurobiological mechanisms underlying PTSD.

Conclusion. While the results of this review suggest potential structural alternations in hippocampal and amygdala subregions in PTSD, more research is needed to specify which subregions are associated with different processes and symptoms of this chronic disorder. Methodological differences, heterogenous populations and publication bias might explain inconsistent results across studies. This review suggest conceptual and methodological ways in which future studies can overcome current barriers, and shed light on the specific roles of these limbic subregions in post-traumatic psychopathology. Consequently, these efforts may pave the way for novel therapeutic strategies for PTSD prevention and treatment[132]–[134].

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Figure Titles and Legends

Figure 1. The hippocampus and amygdala subregions were grouped across all reviewed studies (n=21) based on the well-established literature of their anatomy and function, and on their absolute size, as larger subregions showed greater test-retest reliability across different MRI sites and vendors. These results were generated with FreeSurfer 7.1.0 and are overlayed on an anatomical scan of a single subject. Amygdala nuclei (panel A) and hippocampal subfields (panel B) are displayed in 3D on coronal and sagittal planes, with a black line separating between the two. The amygdala subregions are presented bilaterally, whereas the hippocampal subregions are presented unilaterally.

Figure 2. Flow of information through different phases of the review according to the PRISMA guidelines.

Figures are attached as separate files

Table 1. Characteristics and main findings of the studies included in this review (n=21).

First Author	Country of Study Site	Sample Size (N)[a]	Gender (%males)	Mean Age (years)	Study Groups (n)	Research Design[b]	Trauma Type	PTSD Measures	MRI Field	Subfield Segmentation	Examined Subregions	Main Findings
								A. Hippocampal Subregions Only (n=16)				
Ahmed-Leitao et al. [67]	South Africa	90	53%	34	PTSD (17) SAD with trauma (26) SAD without trauma (22) HC (25)	Cross-Sectional	Early childhood trauma	CTQ	3T	FreeSurfer v6.0	12 unilateral subregions (CA1, CA3, CA4, FIM, GC/ML/DG, HATA, HF, HT, ML, PaSUB, PrSUB, SUB)	Right **PaSUB**, Left **HATA** (PTSD < SAD with/without trauma, HC)
Averil et al. [68]	USA	68	90%	35	PTSD (36) TEC (32)	Cross-Sectional	Combat-exposed veterans	CAPS-IV	3T	FreeSurfer v6.0	10 bilateral subregions (CA1, CA2/3, CA4, DG, PrSUB, SUB, PaSUB, HATA, ML, HT)	More severe PTSD ↔ smaller bilateral **HATA** volume Only in PTSD group: more severe PTSD ↔ smaller bilateral **HATA, CA2/3, CA4** and **ML** volumes
Bonne et al. [69]	USA	44	14%	36	PTSD (22) age- & gender-matched HC (22)	Cross-Sectional	Sexual or physical/emotional abuse, MVA, assault, or robbery[f]	CAPS-IV	3T	Visual assessment by one rater (described in[69])	3 bilateral subregions (Anterior HC, Posterior HC, SUB)	Bilateral **Posterior HC** (PTSD < HC)
Chalavi et al. [70]	Netherlands	61	0%	42	PTSD-DID (17) PTSD (16) HC (28)	Cross-Sectional	Interpersonal traumatizing events (childhood and/or adult life)	CAPS-IV (PTSD Group Only)	3T	FreeSurfer v5.1 + Shape analysis (described in[135])	6 unilateral subregions (CA1, CA2/3, CA4/DG, PrSUB, SUB, FIM)	Bilateral **CA2/3**, Right **CA4/DG**, Left **PreSUB** (PTSD-DID+PTSD < HC) Bilateral **CA2/3**, Bilateral **CA4/DG**, Bilateral **SUB**, Right **CA1**, Left **PrSUB** (PTSD-DID < HC) Left **CA4/DG**, Left **SUB** (PTSD–DID < PTSD)
Chen et al. [71]	USA	282	81%	40	PTSD (142) TEC (140)	Cross-Sectional	Combat-exposed veterans	SCID-IV CAPS-IV or DTS	3T	FreeSurfer v6.0 + Shape analysis (described in[136])	12 unilateral subregions (CA1, CA3, CA4, DG, PreSUB, SUB, PaSUB, HATA, ML, FIM, HT, HF)	Bilateral **CA3**, Left **CA1** (PTSD < TEC), only if the ipsilateral whole hippocampal volume was included as a covariate
Hayes et al. [72]	USA	97	94%	30	PTSD (58) TEC (39)	Cross-Sectional	Combat-exposed veterans	CAPS-IV or PCL-M	3T	FreeSurfer v5.1	5 bilateral subregions (CA1, CA2/3, CA4/DG, PrSUB, SUB)	Bilateral **CA4/DG** (PTSD < TEC) More severe PTSD ↔ smaller **CA4/DG** volume
Luo et al. [74]	China	107	42%	57	PTSD (57) TEC (11) HC (39)	Cross-Sectional	Parents who lost their only child	CAPS-IV	3T	FreeSurfer v5.1	6 unilateral subregions (CA1, CA2/3, CA4/DG, PrSUB, SUB, FIM)	Bilateral **CA2/3**, Bilateral **CA4/DG**, Left **SUB** (PTSD < HC, TEC < HC)
Luo et al. [75]	China	165	40%	57	PTSD (55) TEC (60) HC (50)	Cross-Sectional	Parents who lost their only child	CAPS-IV	3T	VBM using SPM-12 (described in[86])	1 unilateral subregion (Right CA3)	**No volume differences** between groups (PTSD, TEC, HC)
Misaki et al. [76]	USA	72	100%	31	PTSD-NF-Amygdala (20) PTSD-NF-Control (9) HC (43)	Longitudinal (**Pre-** & **Post-**Treatment)	Combat-exposed veterans	CAPS-IV	3T	FreeSurfer v7.1.1	14 unilateral subregions (CA1 head, CA1 body, CA3 head, CA3 body, CA4 head, CA4 body, PrSUB head, PrSUB body, GC-ML-DG head, GC-ML-DG body, SUB head, SUB body, PaSUB head, HATA head)	**No volume differences** between groups at the baseline Left **CA1 head** volume change (increase in PTSD-NF-Amygdala, decreased in PTSD-NF-Control)

First Author	Country of Study Site	Sample Size (N)[a]	Gender (%males)	Mean Age (years)	Study Groups (n)	Research Design[b]	Trauma Type	PTSD Measures	MRI Field	Subfield Segmentation	Examined Subregions	Main Findings
Morey et al. [77]	USA	290[h]	46%	39	PTSD (145) TEC (145)	Cross-Sectional	Combat-exposed veterans or interpersonal violence[i]	SCID-IV CAPS-IV or DTS	3T	FreeSurfer v6.0.0	12 unilateral subregions (CA1, CA2/3, CA4, GC-DG, HATA, FIM, PaSUB, PrSUB, SUB, ML, HF, HT)	Significant interactions between genetic variants and childhood trauma or lifetime PTSD within the **FIM, SUB, CA1,** and **HATA**
Postel et al. [88]	France	148	47%	35	PTSD (53)[3] TEC (39) HC (56)	Cross-Sectional	Terrorist attacks (Paris, France, 2015)	SCID-5 PCL-5	3T	ASHS (described in[137])	4 bilateral subregions (CA1, CA2/3/DG, HT, SUB)	Bilateral **CA2/3/DG, CA1** (PTSD < TEC) Bilateral **CA2/3/DG, CA1, SUB** (PTSD < HC) Only in PTSD group: smaller bilateral **CA1** volume ↔ more severe intrusion symptoms and smaller bilateral **CA2/3/DG** volume ↔ more severe avoidance & hyperarousal symptoms
Suarez-Jimenez et al. [78]	USA	46	28%	40	PTSD (22) Panic Disorder (24)	Cross-Sectional	Patients at Medical Institutes (trauma type not specified)	CAPS-IV SCID-IV	3T	VBM using SPM-12 (described in[86])	2 bilateral subregions (anterior and posterior HC)	Only in PTSD group: For those who received affect-focused treatments, but not exposure-based treatments, smaller **anterior HC** pre-treatment ↔ greater clinical improvement
Szeszko et al. [79]	USA	44	100%	35	PTSD (22) gender-matched TEC (22)	Cross-Sectional	Combat-exposed veterans	CAPS-IV CAPS-5	3T	FreeSurfer v7.1.1	11 bilateral subregions (CA1, CA2/3, CA4, GC-DG, ML, HT, FIM, HATA, SUB, PaSUB, PrSUB)	Bilateral **CA1, CA2/3, CA4, GC-DG, ML, SUB** (PTSD < TEC)
Wang et al. [80]	USA	36	100%	40	PTSD (17) age-matched TEC (14) age-matched HC (5)[d]	Cross-Sectional	Combat-exposed veterans	CAPS-IV SCID-IV	4T	Visual assessment by two raters (described in[138])	4 unilateral subregions (ERC, SUB, CA1, CA3/DG)	Bilateral **CA3/DG** (PTSD<TEC+HC)
Weis et al. [81]	USA	208[c]	45%	33	PTSD (208)[d]	Longitudinal (**T1,T2**=two consecutive days at 2-weeks post-trauma; **T3**=6-months post-trauma)	ED-admitted trauma survivors (Mostly MVA)	CAPS-5 (at T3) Predicting PTSD Questionnaire[139] (at T1)	3T	FreeSurfer v6.0	12 bilateral subregions (CA1, CA3, CA4, PaSUB, PrSUB, SUB, GC-DG, HATA, FIM, ML, HF, HT)	None of the subfield volumes at T1 were prospectively related to PTSD symptoms at T3 None of the subfield volumes at T3 were associated with PTSD symptoms at T3
Yuan et al. [82]	China	142	33%	44	PTSD (69) TEC (73)	Cross-Sectional	Earthquake survivors (Wenchuan, China, 2008)	CAPS-IV SCID-IV	3T	FreeSurfer v6.0	3 unilateral subregions (CA1, CA3, and DG)	More severe PTSD ↔ smaller left **CA3** volume Moderation effect of DRD2 Taq1A polymorphism
B. Amygdala Subregions Only (n=2)												
Morey et al. [84]	USA	355	78%	39	PTSD (n=149) TEC (n=206)	Cross-Sectional	Combat-exposed veterans	CAPS-IV CAPS-5 or DTS	3T	FreeSurfer v6.0 + Shape analysis (described in[140])	9 unilateral subregions (BaA, CeA, LaA, AcBa, MedA, PaLaA, CoA, AAA, CATA)	Bilateral **LaA, PaLa, AcBa** (PTSD < TEC) Left **CeA, MedA, CoA** (PTSD > TEC) Shape analysis: radial distance (anterior amygdala) and Jacobian determinant (posterior amygdala) (PTSD < TEC)
Ousdal et al. [85]	Norway	99	46%	21	PTSD (n=45) TEC (n=54)	Cross-Sectional	Terrorist attacks (Utøya, Norway, 2011)	MINI 6.0.0[141] (Site 1)	3T	FreeSurfer v6.0	6 unilateral subregions (BaA, CeA, LaA, AcBA, MedA, CoA)	More severe PTSD ↔ Smaller volumes of right **LaA, BaA, AcBa, MedA, CeA** Greater symptom reduction ↔ Larger right **LaA** volume

First Author	Country of Study Site	Sample Size (N)[a]	Gender (%males)	Mean Age (years)	Study Groups (n)	Research Design[b]	Trauma Type	PTSD Measures	MRI Field	Subfield Segmentation	Examined Subregions	Main Findings
								PCL-C[142] (Site 2) PTSD-RI[143] (Site 3)				
**C. Both Hippocampus & Amygdala Subregions (n=3)**												
Ben-Zion et al. [12]	Israel	100	44%	33	PTSD Remission (n=71) Non-Remission (n=29)	Longitudinal (**T1, T2,** and **T3** = 1-,6- and 14-months post-trauma)	ED-admitted trauma survivors (Mostly MVA)	CAPS-IV CAPS-5	3T	FreeSurfer v7.1.0	Hippocampus: 4 unilateral subregions (CA1, CA3, DG, SUB) Amygdala: 3 unilateral subregions (LaA, BaA, CeA)	Smaller bilateral **SUB** and right **CA1** at T1 (PTSD Remission>Non-Remission) No time-dependent longitudinal changes (T1 to T2 to T3) in of the subregions
Koch et al. [73]	Netherlands	221	73%	24	Symptom increase (n=35) Symptom decrease (n=46) No change (n=140)[e]	Longitudinal (**Baseline** & 16- months **follow-up**)[g]	Police recruits exposed to potentially traumatic events	PCL-5 CAPS-5 (only at Follow-up)	3T	FreeSurfer v6.0	Hippocampus: 3 unilateral subregions (CA1, CA3, DG) Amygdala: 4 unilateral subregions (BaA, CeA, LaA, MedA)	Smaller left **DG** volume at baseline ↔ more severe PTSD at follow-up More police-related traumatic events ↔ increase in left **BaA** volume from baseline to follow-up
Zhang et al. [83]	China	201	32%	42	PTSD (n=69) TEC (n=76) HC (n=56)	Cross-Sectional	Earthquake survivors (Wenchuan, China, 2008)	CAPS-IV SCID-IV	3T	FreeSurfer v6.0	Hippocampus: 12 unilateral subregions (CA1, CA3, CA4, FIM, GC/ML/DG, HATA, HF, HT, ML, PaSUB, PrSUB, SUB; divided to hippocampal head and body when applicable) Amygdala: 9 unilateral subregions (BaA, CeA, LaA, AcBa, MedA, PaLaA, CoA, AAA, CATA)	Right **PrSUB**, Left **MedA** (PTSD > TEC) Left **CA3, CA4, GC/ML/DG, PrSUB, FIM, HATA, HT, AcBa, CeA, CoA, CATA**; Right: **HT, CA3, CA4, GC/ML/DG, ML, SUB, HT, HF, BaA, AcBa, CeA, MedA, CoA** (PTSD=TEC<HC) More severe PTSD ↔ Smaller right **AcBA, ML** Only in PTSD Group: More severe PTSD ↔ Smaller right **CoA** Only in TEC Group: More severe PTSD ↔ Larger right **CoA**

Hippocampal Subregions
CA= cornu ammonis
DG =Dentate Gyrus;
FIM = Fimbria
GC-DG = Granule Cell layer of Dentate Gyrus
HATA = Hippocampal–Amygdala Transition Area
HF = Hippocampal Fissure
HT = Hippocampus Tail
ML = Molecular Layer
PaSUB = Para-subiculum;
PrSUB = Pre-subiculum;
SUB = Subiculum;

Amygdala Subregions
BaA = Basal Amygdala
CeA = Central Amygdala
LaA = Lateral Amygdala
AcBa = Accessory Basal Amygdala
MedA = Medial Amygdala
PaLaA = Paralaminar Amygdala
CoA = Cortical Amygdala
AAA = Anterior Amygdaloid Area
**CATA** = Cortico-Amygdaloid Transition Area

Other Abbreviations
ASHS = automatic segmentation of hippocampal subfields
CAPS = clinician-administered PTSD scale
CTQ = childhood trauma questionnaire
DTS = Davidson trauma scale
ED = emergency department
ERC = Entorhinal Cortex
HC = healthy controls
MVA = motor-vehicle accident
NF = neurofeedback
PCL = PTSD checklist;
PTSD = post-traumatic stress disorder
PTSD-DID = PTSD with dissociative identity disorder
PTSD-NF = PTSD patients who underwent neurofeedback targeting the amygdala (PTSD-NF-Amygdala) or a control region (PTSD-NF-Control)
SAD = seasonal affective disorder
SCID = structured clinical interview for DSM
SPM = statistical parameter mapping
TEC = trauma-exposed controls
USA = united states of America
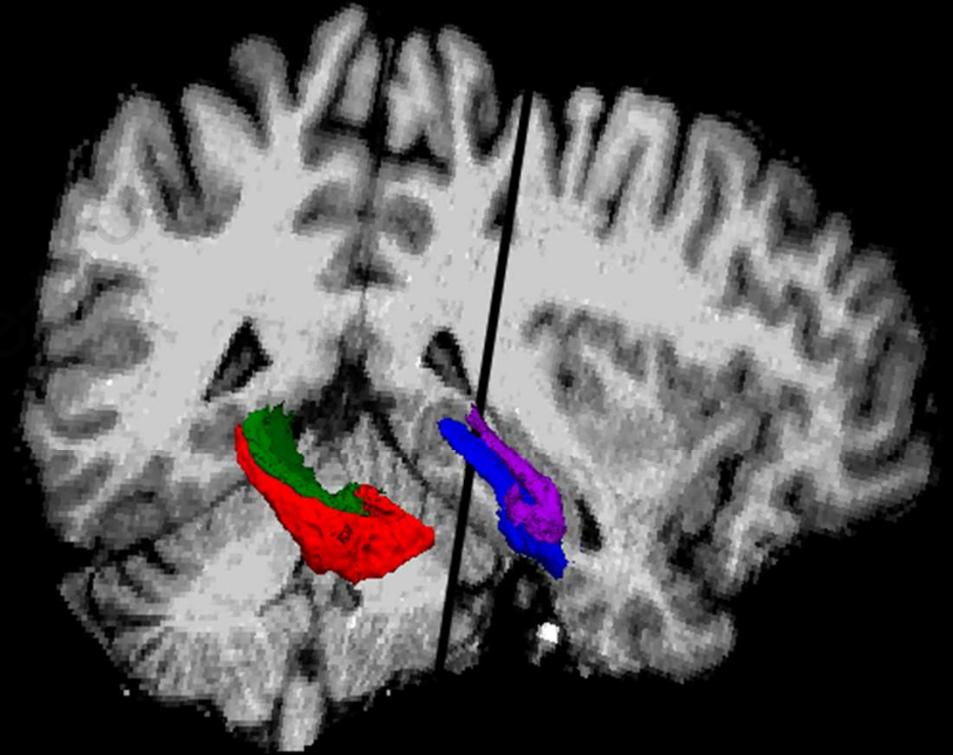**VBM =** voxel-based morphometry

Notes
(a) Refers to the total amount of subjects examined, before exclusion (e.g., dropouts, missing data, poor quality data)
(b) Refers to the number of MRI assessments (and not clinical assessments). All studies with a single MRI scan are considered cross-sectional, and those with more than one MRI scan are considered longitudinal.
(c) The authors combined full PTSD and partial PTSD (re-experiencing + one other cluster) into one PTSD group.
(d) All individuals met criterion A of DSM-5 and scored a minimum of three on the Predicting PTSD Questionnaire.
(e) Analysis of symptom change was conducted based on the PCL scores (follow-up compared to baseline), dividing participants into three groups: symptom increase, symptom decrease, and no symptom change.
(f) Half of the subjects (n=11) suffered from prolonged prepubertal trauma: sexual, or physical/emotional abuse. The other half (n=11) underwent a single trauma in adulthood: sexual assault, MVA, or assault/robbery.
(g) Baseline assessment took place while recruits were in a safe school environment at the police academy. A follow-up assessment took place 16 months later, after the emergency aid services training which included exposure to potentially traumatic events.
(h) Included 2 independent samples: Mental Illness Research Education and Clinical Centre (MIRECC), and Grady Trauma Project (GTP).
(i) MIRECC sample: military veterans with high levels of trauma in the military (in some cases during childhood/adolescence). GTP sample: civilian women with high rates of sustained trauma and interpersonal violence (in some cases during childhood/adolescence).

A.

B.
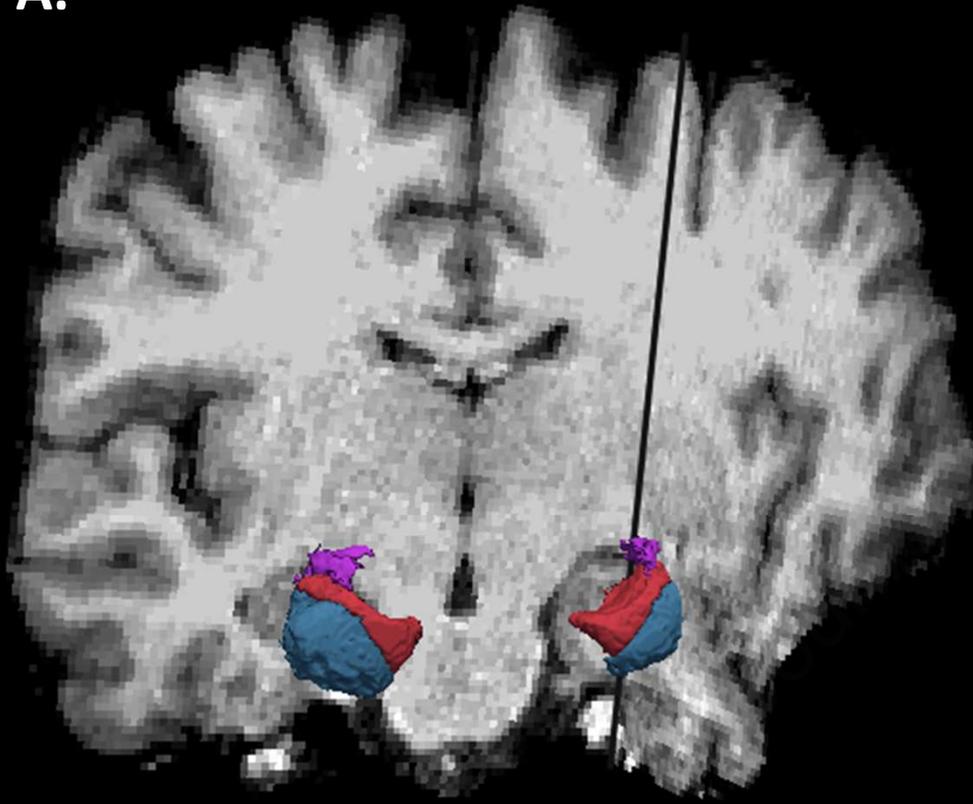
● Lateral Amygdala
● Basal Amygdala
● Central Amygdala

● CA3
● CA1
● Subiculum
● Dentate Gyrus

Identification of studies via databases

Identification

Records identified from databases (n = 3513)

Duplicate records removed *before screening* (n = 1824)

Screening

Records screened (n = 1689)

Records excluded (n = 1570)

Reports sought for retrieval (n = 119)

Reports not retrieved (n = 0)

Reports assessed for eligibility (n = 119)

Reports excluded (n=98)
  42 No PTSD assessment
  25 No subregions volume
  12 Conference abstract
  7 Non-adult participants
  5 TBI or head injury
  4 Review articles
  3 Animal studies

Included

Studies included in review (n = 21)