Grey Matter Volume Reductions of the Left Hippocampus and Amygdala in PTSD: A Coordinate-Based Meta-Analysis of Magnetic Resonance Imaging Studies

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Keywords

Posttraumatic stress disorder · Morphometry · Magnetic resonance imaging · Amygdala · Hippocampus

Abstract

Introduction: In recent years, research on posttraumatic stress disorder (PTSD) focused on the description of different biological correlates of illness. Morphological changes of different brain regions were involved in PTSD neurophysiopathology, being related to trauma or considered a resilience biomarker. In this meta-analysis, we aimed to investigate the grey matter changes reported in magnetic resonance imaging (MRI) studies on patients who have developed PTSD compared to exposed subjects who did not show a clinical PTSD onset. **Methods:** We meta-analysed eight peer-reviewed MRI studies conducted on trauma-exposed patients and reported results corrected for false positives. We then conducted global and intergroup comparisons from neuroimaging data of two cohorts of included subjects. The in-

cluded studies were conducted on 250 subjects, including 122 patients with PTSD and 128 non-PTSD subjects exposed to trauma. **Results:** Applying a family-wise error correction, PTSD subjects compared to trauma-exposed non-PTSD individuals showed a significant volume reduction of a large left-sided grey matter cluster extended from the parahippocampal gyrus to the uncus, including the amygdala. **Conclusions:** These volumetric reductions are a major structural correlate of PTSD and can be related to the expression of symptoms. Future studies might consider these and other neural PTSD correlates, which may lead to the development of clinical applications for affected patients.

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Introduction

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1], defines posttraumatic stress disorder (PTSD) among trauma- and stressor-re-

lated disorders. PTSD consists of psychopathological symptoms that follow a severely traumatic experience, including affective symptoms, intrusive memories of trauma, avoidance of trauma-related events, hyperarousal, and negative cognitions and mood.

Although traumatic events are common globally, there is a lack of comprehensive data on the epidemiology of PTSD in the global population. The cross-national lifetime prevalence of PTSD is 3.9% in total and 5.6% among those individuals exposed to traumatic experiences, varying for geographic provenience and social background [2].

In more than half of the cases, the clinical picture is complicated by the presence of comorbidities, including anxiety and mood disorders, and substance use disorder [3]. Furthermore, patients with PTSD can have an increased risk of suicide [4].

The economic impact on health systems and the indirect costs due to the disease are substantial [5]. This could be of crucial importance in the current period in which the COVID-19 pandemic produces symptoms of PTSD in survivors of COVID of up to 40% of cases [6]. National lockdowns and other restrictions to halt the SARS-CoV-2 spread frequently correlated with PTSD-like symptoms in the population [7]. During the COVID-19 pandemic, the urgency of acquiring knowledge about PTSD appears of utmost importance. Most patients with COVID-19 have experienced posttraumatic stress symptoms, which significantly increases the probability of developing PTSD [8]. Other evidence about coronavirus pandemics, severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19 showed a particularly high risk for PTSD occurrence among emergency healthcare workers [9]. Also, a higher occurrence of PTSD symptoms was related to indirect stressors, including forced quarantine and nationwide lockdowns, which became prevalent in the population during the pandemic outbreak, with a relevant trend in young adults [10]. Furthermore, there is evidence of overlapping relationships between severity of inflammation during acute COVID-19, changes in the structure and function of the brain, and severity of depressive and posttraumatic symptoms in survivors [11].

In recent years, research on PTSD focused on the description of the biological mechanism underlying the disorder. The biological correlates of PTSD have been studied with different methods and techniques, although without defining a unitary etiopathogenetic [12]. Although an in-depth understanding of the neurobiology of

PTSD has yet to be clarified, the last 2 decades have seen rapid growth in the study of PTSD using neuroimaging techniques [13].

Morphological changes of other brain regions were involved in PTSD neurophysiopathology, including the prefrontal cortex and dorsal anterior cingulate cortex, of which reduced volume may be correlated with the trauma [14] or may constitute a resilience biomarker [15]. Studies using diffusion tensor imaging technology hypothesized an impaired inhibitory interaction between the ACC and amygdala in PTSD [16, 17].

The same grey matter areas showing PTSD-related structural alterations also showed functional changes in functional neuroimaging studies. Resting-state functional MRI studies showed alterations in spontaneous neuronal activity in both amygdala and ACC. Other neural activity changes were found in the dorsolateral and ventromedial prefrontal cortex, inferior frontal gyrus, insula, hippocampus, parahippocampus, and parietal and temporal cortices [18]. Besides, it is debated whether these alterations are a consequence of the PTSD onset or may indicate a premorbid trait, i.e., an index of vulnerability [19].

Different models linked PTSD processes to morphometric changes of the brain [20, 21], and existing meta-analyses on grey [22, 23] and white matter [17, 24] in patients with PTSD showed several anatomical correlates of this disorder. However, there is a lack of meta-analyses of studies on subjects exposed to trauma that developed PTSD versus trauma-exposed subjects who did not develop PTSD, using a coordinate-based approach for assessing grey matter changes in PTSD.

In this meta-analysis, we intended to investigate the morphological brain changes in MRI studies focused on patients who have developed PTSD following exposure to severe trauma or extreme events, compared to exposed subjects who did not show the clinical onset. This study hypothesizes that subjects exposed to severe trauma who developed PTSD compared to subjects who did not develop PTSD might show significant volume reductions at the cortical and subcortical levels.

The main objective of this study was to deepen knowledge on the pathophysiological correlates of PTSD that may be helpful for the clinical assessment and personalized therapeutic interventions. Furthermore, the evidence of neural structural correlates of PTSD onset may be useful in identifying potential endophenotypes of this disorder, as well as the absence of such correlates could be indicative of resilience.

Fig. 1. PRISMA search strategy.

Materials and Methods

A search was conducted on 18 November 2021 using the international scientific database PubMed (<http://www.pubmed.gov>) to identify peer-reviewed magnetic resonance imaging (MRI) studies that analysed cortical volume in patients with PTSD and subjects exposed to trauma that did not develop PTSD. We followed the methods of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) [24].

We searched the database PubMed using the keywords “PTSD,” “Post-Traumatic Stress Disorder,” “magnetic resonance imaging,” “MRI,” “grey matter,” and “gray matter.” Besides, we have collected further studies by examining the bibliographies of relevant articles in the first step or through the “related article” function of the PubMed database and bibliographies of reviews on the topic.

We included articles of MRI studies using a voxel-based morphometric approach in samples of patients diagnosed with PTSD compared to non-PTSD subjects exposed to trauma. Furthermore, only studies that report results corrected for false positives were considered. We excluded studies that used neuroimaging techniques other than MRI, use of an ROI approach, studies without detailed coordinates according to the reference system of the Neurological Institute of Montreal (MNI) [25] or Talairach [26], lack of a control sample of non-PTSD subjects exposed to trauma, studies that did not perform a correction for false-positive results, and twin studies.

Based on these criteria, we analysed 113 studies, from which we excluded 105 studies, finally including 8 studies published before 2018 [27–34]. We report the search flow diagram in Figure 1.

We created a database with the coordinates of the studies referred to the contrast PTSD versus non-PTSD by volume of the

Table 1. Studies included in the meta-analysis and characteristics of samples

Study	Coordinate system	PTSD sample, <i>n</i> (m, f)	Mean age, years (SD)	Illness duration, years	On meds (anti-depressants)	Trauma-exposed non-PTSD sample, <i>n</i> (m, f)	Mean age, years (SD)
Li et al. [27]	TAL	12 (4, 8)	34.56 (4.91)	0.42	0	12 (4, 8)	33.25 (5.27)
Nardo et al. [28]	TAL	21 (15, 6)	41.7 (9.4)	2.5	0	22 (16, 6)	40.8 (8.9)
Nardo et al. [29]	MNI	15 (12, 3)	43.33 (8.35)	0.4	6.67%	17 (11, 6)	41.59 (9.04)
O'Doherty et al. [30]	MNI	25 (12, 13)	34 (8.4)	4.61	68%	25 (12, 13)	31.7 (6)
Rocha-Rego et al. [31]	MNI	16 (7, 9)	43.3 (5.78)	3	100%	16 (7, 9)	44.9 (6.6)
Sui SG et al. [32]	MNI	11 (0, 11)	25.55 (4.01)	11	0	8 (0, 8)	27.5 (4)
Tan et al. [33]	MNI	12 (12, 0)	37.6 (3.7)	<0.08	0	14 (14, 0)	40.9 (5.2)
Zhang J. et al. [34]	MNI	10 (10, 0)	40.8 (6.83)	0.5	0	10 (10, 0)	34.3 (5.37)

MNI, Montreal Neurological Institute; SD, standard deviation; TAL, Talairach.

Table 2. Brain regions with reduced volume in patients with PTSD versus trauma-exposed subjects who did not develop PTSD, MNI coordinates

Cluster No.	<i>x</i>	<i>y</i>	<i>z</i>	ALE	FWE <i>p</i>	<i>Z</i>	Area (nearest grey matter, 5-mm range)
1	-18	-4	-24	0.011706093	2.16E-05	4.0897985	Left hemisphere, limbic lobe, parahippocampal gyrus, amygdala
	-24	-12	-28	0.011320721	2.69E-05	4.03879	Left hemisphere, limbic lobe, parahippocampal gyrus, hippocampus

ALE, activation likelihood estimation; FWE, family-wise error.

grey substance. Then, we performed a single analysis of the data set with the Brainmap GingerALE 3.0.2 software (<http://www.brainmap.org/ale/>).

Data processing and statistical analysis: the coordinates in the Talairach space have been converted to the MNI space with the online utility Bioimage Suite (<http://sprout022.sprout.yale.edu/mni2tal/mni2tal.htm>), so that all coordinates in this study are MNI. The meta-analyses were based on the ALE method, using the GingerALE 3.0.2 algorithm (<http://www.brainmap.org/ale/>) [35, 36].

We used the corrected threshold for cluster-level inference. We used an uncorrected *p* value of 0.001 as the cluster formation threshold and a *p* value of 0.05 for cluster-level inference (correction for false-positive results). The images obtained were visualized using the Mango software (<http://ric.uthscsa.edu/mango/>) and superimposed on an anatomical model.

Results

Global analysis of all studies: the included studies were conducted on 250 subjects, divided into 122 patients with PTSD (72 men, 50 women, average age: 37.9 years, SD = 6.62) and 128 non-PTSD subjects exposed to trauma (74 men, 54 women, average age: 37.09 years, SD = 6.53). The meta-analysis included eight experimental procedures

(44 foci) that reported significant volume reductions in patients compared to non-PTSD subjects exposed to trauma. We summarize the sociodemographic and clinical characteristics of the study sample in Table 1.

Between-group analysis: subjects with PTSD, compared to subjects exposed to trauma who did not develop PTSD, showed a significant volume reduction of a large cluster extending from the left parahippocampal gyrus (70.3%) to the left uncus (29.7%). This cluster included the Brodmann's area (BA) 34 (54.1%), amygdala (29.7%), BA 28 (8.1%), hippocampus (5.4%), and BA 35 (2.7%) (Table 2; Fig. 2). We summarize the study results in Table 2.

Discussion

This study showed significant left-sided volume reductions in the amygdala, entorhinal cortex (BA 28 and BA 34), subgenual gyrus (BA 35), and hippocampus in patients with PTSD compared to subjects exposed to severe trauma who did not develop PTSD. These results are in line with existing evidence and offer further perspectives in the investigation of PTSD [23, 37, 38]. This grey matter deficit profile affects brain networks involved in

emotional processing and regulation and fear extinction, which are known to be involved in PTSD.

Our results are in line with different evidence of the involvement of the hippocampus-amygdalar complex in the neurophysiopathology of PTSD [39]. Both amygdala and hippocampus are known to consolidate and maintain contextual fear memories and may be involved in the treatment response of fear-based pathologies [40]. A smaller hippocampal volume has been considered a risk factor to develop PTSD in women exposed to a sexual assault [41], and hippocampal damage and dimensional alterations were involved in episodic memory disturbance and mind wandering [42]. Furthermore, the integrity of the amygdala has been inversely correlated with the degree of severity of PTSD [43–46] and directly correlated with the treatment response [47].

Akiki et al. [38] studied the morphometric correlates of PTSD symptoms with the vertex-wise shape method, showing inverse correlations between the symptom severity and vertices of the amygdala and hippocampus. The same study underlined correlations between hippocampal and amygdala shape and PTSD symptoms; all symptom clusters have been significantly associated with indentations in both structures.

Our results can be compared to evidence deriving from several functional neuroimaging studies of PTSD showing that the hippocampus and amygdala can undergo important changes in their activity. For example, decreased NAA/Cr ratio has been associated with alterations in the turnover of the cell membranes of the hippocampus, which, in turn, may be related to specific PTSD symptoms, including avoidance and re-experiencing [48]. Patients with PTSD compared to HCs showed reduced within-DMN functional connectivity between the posterior cingulate cortex and occipital cortex; furthermore, increased connectivity between the posterior cingulate cortex and hippocampus was associated with increased trauma severity and anxiety [49]. Shin et al. [50] showed that the symptom severity of PTSD has been positively associated with the rCBF of the hippocampus and parahippocampal gyrus, and the provocation of PTSD symptoms correlated with increased rCBF in the amygdala in veterans with PTSD [44]. Other BOLD functional MRI studies showed a direct correlation of PTSD severity and emotional reactivity with increased amygdala activation, mainly left-sided [43, 44]. The right-sided amygdalar hyperactivation in PTSD might relate to the volumetric asymmetry that we found, in line with other evidence [51], although it could be a specific and independent functional correlate of PTSD.

Fig. 2. Significantly reduced volume of the left hippocampus/amygdala (red/orange areas) in patients with PTSD versus trauma-exposed subjects who did not develop PTSD.

In our meta-analysis, the volumetric reduction of the left amygdala-hippocampus complex can be related to functional connectivity changes; altered interconnection with the hippocampus may have a crucial role in the related emotional processing. Other connectivity changes were reported between amygdalar nuclei, prefrontal cortices, and angular gyri [52], demonstrating the importance of amygdalar dysfunction in PTSD.

PTSD-related volumetric changes were found to be possibly reverted after successful drug treatment, especially with the use of selective serotonin reuptake inhibitors (SSRIs) [53], which has been also stressed in MRS animal studies on fluoxetine [54]. This evidence suggested the possible reversibility of the volumetric reduction. Con-

versely, there is evidence of lack of volumetric recovery in the hippocampus in patients with PTSD treated with SSRIs [53, 55], despite a reported improvement in the nerve growth factor levels after treatment with escitalopram [53]. PTSD-related volumetric changes were also found to be correlated to the treatment outcome of different psychological interventions, mainly at the hippocampal level [56]. Furthermore, our results are in line with existing recent evidence that showed major structural brain changes in COVID-19 survivors [11], in whom the volumes of the left hippocampus and amygdala have been negatively correlated with the severity of psychiatric symptoms [57].

Limitations

The results of this meta-analysis should be viewed with caution, given the following limitations. The main limitation is the low number of the included studies; however, we included only studies with results corrected for false positives and performed a further FWE correction, which gave a strong statistical relevance to our results. A further limitation is the inclusion of subjects with different types of traumata in a single sample, although traumatic experiences were all similar events. Furthermore, the inclusion of studies focused on samples with different medications, psychological treatment, and course of illness may have affected the results.

Conclusions

This study underlined the importance of the left-sided volume reductions of the hippocampus and amygdala in patients with PTSD compared to subjects exposed to severe trauma that did not develop PTSD. The volume re-

duction of the hippocampus may relate to intrusive memories and mood changes/emotional disorders. The volume reduction of the left amygdala may be involved in hyperarousal and avoidance behaviours of trauma-related events. Given the improvement in PTSD symptoms after pharmacological treatments and other interventions, further studies are needed to demonstrate the possible reversibility of the reported cortical volume reduction after treatment. A better understanding of PTSD morphometric correlates may lead to the development of clinical applications for affected patients.

Conflict of Interest Statement

In the last 3 years, A.D.C. has received lecture or advisory board honoraria or engaged in clinical trial activities with Imagine/Edra, GlaxoSmithKline, and Fidia, which did not influence the content of this article. In the last 3 years, M.P. has received lecture or advisory board honoraria or engaged in clinical trial activities with Angelini, Lundbeck, Janssen, Otsuka, Italfarmaco, and Allergan, which did not influence the content of this article. All other authors report no biomedical financial interests or potential conflicts of interest.

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Author Contributions

Conceptualization, A.D.C. and S.F.; methodology, A.D.C. and S.F.; data curation, A.D.C., S.F., F.C., and T.Z.; writing – original draft preparation, A.D.C., F.C., and S.F.; writing – review and editing, all authors; supervision, M.P., A.D.C., and S.F.

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