Degree project

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Gray Matter Alterations in Individuals with PTSD Compared to Controls: A Systematic Review

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Abstract

This systematic review aims to investigate the alterations in gray matter volume (GMV) observed in the brains of individuals diagnosed with post-traumatic stress disorder (PTSD) through the Clinical Administered PTSD scale (CAPS) using Voxel-Based Morphometry (VBM) as a method. PTSD is diagnosed when an individual meets all the criteria for PTSD as defined by the DSM, which includes having experienced or witnessed a traumatic event, experiencing intrusive symptoms such as flashbacks or nightmares, avoiding triggers related to the trauma, experiencing negative changes in mood and cognition, and experiencing changes in arousal and reactivity. Previous research investigating gray matter alterations in patients with PTSD has yielded heterogeneous findings. The review incorporates a comprehensive search and analysis of pertinent studies conducted between 1995 and the present. Diverse databases were scrutinized to identify articles that fulfilled the inclusion criteria. Ultimately, a total of seven articles meeting our inclusion criteria were included in this systematic review. The sample sizes ranged from 30 to 75 participants. The control groups in the chosen articles varied, some only had healthy controls (HC), while some had trauma-exposed controls (TC) or included both. The results consistently revealed a reduction in GMV predominantly in the hippocampus, with additional areas exhibiting decreased GMV such as the bilateral hypothalamus and left inferior parietal lobule, right middle temporal gyrus, right inferior temporal gyrus, and right fusiform gyrus, as well as the bilateral calcarine cortex, left dorsal anterior cingulate cortex, left anterior cingulate cortex, and bilateral insula.

Keywords: Post-traumatic stress disorder, PTSD, Voxel-Based Morphometry, gray matter

Gray Matter Alterations in Individuals with PTSD Compared to Controls:

A Systematic Review

Introduction

Post-Traumatic Stress Disorder (PTSD) is an anxiety disorder that can occur after a person experiences or witnesses a traumatic event. A range of incapacitating psychological, physical, and cognitive symptoms are commonly associated with PTSD, a condition that could be significantly debilitating (O'Doherty et al., 2017).

Based on several historical anecdotes, a notable set of maladaptive symptoms emerged among soldiers who participated in the First World War. The symptoms were determined to be directly linked to their wartime experiences. The soldiers experienced physical issues like extreme fatigue, sensory impairment, confusion, and nightmares, without any apparent medical explanation, and they named it “Shell Shock.” Although the symptoms of Shell Shock initially appeared to be primarily physical, they were ultimately recognized as being rooted in psychological trauma that had been repressed (American Psychiatric Association, 2013).

Full-threshold PTSD is diagnosed when an individual meets all the criteria for PTSD as defined by the DSM, which includes having experienced or witnessed a traumatic event, experiencing intrusive symptoms such as flashbacks or nightmares, avoiding triggers related to the trauma, experiencing negative changes in mood and cognition, and experiencing changes in arousal and reactivity. Several indications suggest that subthreshold forms of PTSD are more common later in life than full-threshold PTSD. For instance, individuals with subthreshold PTSD may have experienced a traumatic event and exhibit some of the symptoms of PTSD, like intrusive thoughts or avoidance behavior, but not fulfill all the criteria necessary for a full PTSD diagnosis. This could mean the symptoms are not intense enough to cause significant distress or hinder their regular activities (American Psychiatric Association, 2013).

One way to diagnose patients with PTSD is through the Clinical Administered PTSD Scale (CAPS). CAPS is a structured diagnostic interview for PTSD, which is used widely and is acknowledged as a valid assessment scale (Weathers et al., 2018). At the time, the PTSD criteria were revised in the Diagnostic and Statistical Manual of Mental Disorders (DSM–5; American Psychiatric Association, 2013) so were CAPS. The goals of the CAPS revision were to correspond with the new PTSD criterion in DSM-5 (DSM–5; American Psychiatric Association, 2013).

When revising the scale, researchers investigated the literature and gathered critiques previous CAPS users lifted, as well as what CAPS authors and their colleagues had to say (Weathers et al., 2018).

The American Psychiatric Association (2013) mentions the key component of PTSD is the presence of characteristic symptoms that arise in response to exposure to one or more traumatic events. The clinical manifestation of PTSD can vary widely among individuals. Some people may experience predominantly fear-based emotional, and behavioral symptoms, while others perhaps most troubled by anhedonic or dysphoric mood states and negative thought patterns. Among individuals with PTSD, arousal and reactive-externalizing symptoms may be more salient for some, whereas dissociative symptoms may be more prevalent for others. Individuals with PTSD often display externalizing behaviors as a way to express their emotional dysregulation and distress. Such behaviors may include impulsivity, aggression, acting out, and hostility directed toward others or their surroundings. Additionally, some individuals with PTSD may exhibit a combination of these symptom patterns (American Psychiatric Association, 2013). People with PTSD can re-experience traumatic events in different ways. Re-experiencing traumatic events refers to the involuntary recurrence of intense distressing memories or feelings related to a traumatic event. It is common for them to have recurrent, involuntary, and intrusive recollections of the traumatic event. A distressing dream is also a common re-expressing symptom. Additionally, an individual may experience a dissociative state, where the person behaves as if the traumatic event reoccurs at that moment. It can last from a few seconds to several days. Traumatic events can negatively affect individuals' moods or cognition. In addition, the negative effect, due to PTSD, can emerge in various ways, such as an inability to remember important aspects of the traumatic events, having unrealistic negative expectations concerning oneself, impaired attention and concentration ability, and disturbance in information processing (Scott et al., 2015). Finally, individuals with PTSD are highly prone to having suicidal ideation and making suicide attempts (American Psychiatric Association, 2013).

The prevalence of PTSD in the United States, using DSM-IV criteria at age 75 years, is 8.7%, and about 3.5% regarding twelve-month prevalence among U.S. adults. This prevalence is estimated lower in European countries, at an estimate of 6% of the Swedish population (Kayhan., 2019), and in most Asian, African, and Latin American countries, approximately 0.5% – 1.0% (American Psychiatric Association, 2013).

There is a significant link between cultural groups and the development of PTSD. The incidence of PTSD is more significant in individuals who have served in the military or have occupations that increase the likelihood of experiencing traumatic events (American

Psychiatric Association, 2013). The occurrence of PTSD can vary depending on the developmental stage. Children generally tend to have a lower prevalence of PTSD after exposure to severe trauma. Older adults appear to have a lower prevalence of full-threshold PTSD compared with the general population.

The incidence of PTSD is more common in women than in men. The higher prevalence of PTSD in females can be partly explained by their greater chances of experiencing traumatic events like sexual assault and other forms of interpersonal violence. Notably, gender differences are insignificant within populations exposed specifically to such stressors (American Psychiatric Association, 2013).

Individuals who suffer from PTSD have an 80% greater likelihood of experiencing other symptoms such as depression, bipolar disorder, anxiety disorder, or substance use disorders (American Psychiatric Association, 2013). Finally, there is a significant overlap between PTSD and major neurocognitive disorders and some symptoms are common among these disorders. These major neurocognitive disorders include anxiety disorder, acute stress disorder, psychotic disorder, and personality disorder (American Psychiatric Association, 2013). In Spinhoven et al. 's (2014) study, the prevalence of PTSD among anxiety and depressive disorders over a period of 5 years was 9.2% and the comorbidity was particularly high in major depressive disorder (MDD) (84.4%). Another study by Flory and Yehuda (2015) suggested that about half of the people with PTSD also suffer from MDD. From these results, one can draw the conclusion that the comorbidity is high, particularly in MDD. A study by Serra-Blasco et al. (2021) suggested that the high comorbidity between MDD, PTSD, and anxiety disorder (ANX) has inhibited the research of their neural correlates. In the study, they conducted a meta-analysis of literature comparing specific and typical GMV characteristics of three groups (PTSD, MDD, and ANX) with healthy controls (HC).

The behavioral observations of PTSD may imply that certain brain areas are involved. In a study by Sherin and Nemeroff (2011), they state that the characteristic changes in brain function in patients with PTSD are related to the areas that are associated with adaptation to stress and fear conditioning. For example, the hippocampus, amygdala as well as cortical regions including the anterior cingulate, insula, and orbitofrontal region, all play their part in interconnecting to form a neural circuit that among other functions mediates adaptation to stress and fear conditioning. Sherin and Nemeroff (2011) also describe the reduced hippocampal volume as a defining trait of PTSD. Expectedly, the hippocampus is involved in the control of stress responses, declarative memory, and contextual aspects of fear conditioning, it is also one of the most plastic regions in the brain (Sherin & Nemeroff., 2011). When investigating other literature on the subject, several neuroimaging studies have revealed that recent onset PTSD is associated with decreased gray matter volume (GMV) in

limbic structures (Wignall et al., 2004). Compared to HC, Hakamata et al. (2007), discovered that individuals who developed PTSD demonstrated reduced GMV in specific brain regions, such as the left lingual gyrus, left parahippocampal gyrus, bilateral posterior cingulate, and left precuneus. Similarly, Zhang et al. (2011) found notable gray matter reductions in the left hippocampus and left parahippocampal gyrus among both HC and individuals with PTSD.

The aim of our study is to understand the neural alterations in PTSD and to contribute to a broader understanding of which areas that get affected by PTSD. Tan et al. (2013) described how previous PTSD imaging studies have failed to clearly describe PTSD symptoms. Tan et al. (2013) also highlights that the brain structure of patients with PTSD inevitably changes as PTSD progresses. Thus, it has been difficult to chart the different changes in brain structure (Tan et al., 2013).

To conduct this study, we examined studies that use Voxel-Based Morphometry (VBM) and how the method has been used in studies about PTSD diagnosed through CAPS to determine the differences in GMV compared to controls. VBM as a method was first introduced in 1995 by Wright et al. (1995) in a paper covering techniques for characterizing cerebral white and gray matter differences and is today a commonly used method (Zhang et al., 2011). Later in 2000, Ashburner and Friston (2000) formally introduced VBM as a quantitative method used to compare the volume of areas by taking into account the amount of gray matter, white matter, and cerebrospinal fluid present, resulting in an accurate representation of changes in the structure of brain tissue (Ashburner & Friston., 2000).

In this study, we have compiled results from seven articles that fulfilled our inclusion criteria in order to find out how GMV differs between PTSD patients and controls. The study is conducted with the aim to find contributions to the research in PTSD and how GMV differs between PTSD patients and controls.

Methods

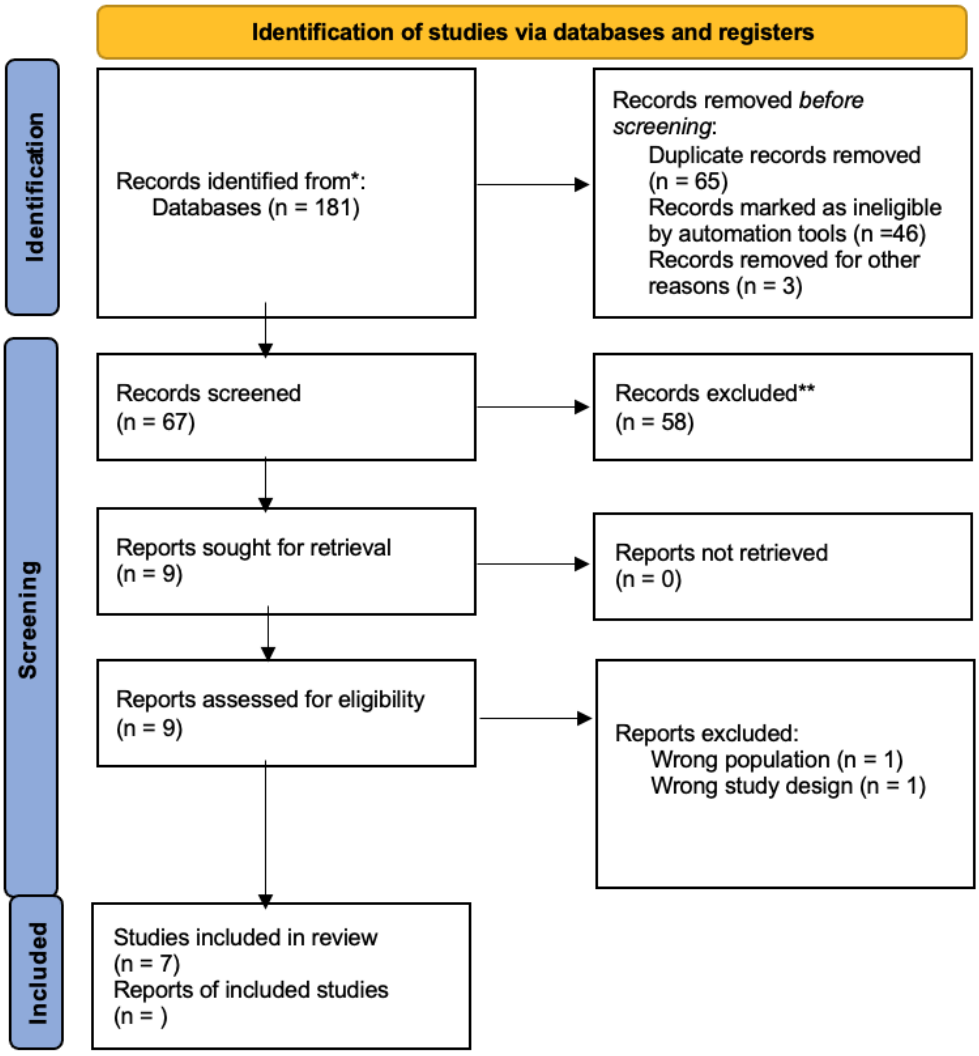
The studies included, compare adult individuals with PTSD assessed through CAPS with controls using VBM. In our systematic review, we include both men and women and specifically adults, since PTSD tends to differentiate between adults and children (DSM–5; American Psychiatric Association, 2013). All the studies we look for will also be in the English language since this is the most used academic and scientific language (Altbach., 2007). We have also decided to exclude any comorbidities. Furthermore, we decided to include the literature after 1995, since that was the year the method VBM was first introduced (Wright et al., 1995).

We used Web of Science, Medline EBSCO, and PubMed to collect articles. We then searched these databases with our chosen keywords using the above criteria.

When searching in databases on the 21st of February 2023, we used the following search string (ptsd OR post*traumatic stress disorder) AND (VBM OR voxel*based morphometry. This gave us 86 results in PubMed, 37 in Medline EBSCO, and 58 in Web of Science. Both authors of this study compiled the studies, and the choice of articles was further discussed with the supervisor. We had an open dialogue about it, such as any disagreements requiring that both or all three persons involved agreed. Our selection process consisted of searching for articles about PTSD diagnosed through CAPS using VBM methods to compare GMV with controls.

We exported the results of our search from the databases to Rayyan (Ouzzani et al., 2016), where some of them were marked as ineligible by automation tools due to their title; for example, “animal study”. In the next step, we removed all the duplicated articles. We then scrutinized the articles by titles, and ended up excluding 58 of them. Furthermore, we phased out further articles by reading the abstract, which left us with nine articles. Finally, after reading the remaining articles full contents, we excluded one of the articles due to it having the wrong population because it contained one or more comorbid disorders. Which left us with eight articles that included our eligibility criteria. However, later on, we removed one more article because we earlier failed to recognize that they were investigating gray matter density (GMD) instead of GMV. This left us with a total of seven articles.

PRISMA flow chart



Results

Sample size and participants

The aim of our review is to find studies which have investigated alterations of GMV in individuals with PTSD compared to control groups. According to our inclusion criteria, we have selected seven studies to understand the association between PTSD and GMV in the brain. The total number of participants included in our systematic review, derived from multiple studies, amounted to 307 individuals. The sample sizes within these studies varied from 30 to 75. All participants were evaluated using CAPS as a means of identifying individuals with PTSD and ensuring their inclusion in the respective studies.

Studies and results

The study by Chen et al. (2012), investigated the variation in GMV in specific brain regions between individuals who had experienced a single prolonged trauma diagnosed with recent onset PTSD and those who did not develop PTSD. The experiment included 20 trauma survivors, with (n = 10) and without (n = 10) recent onset PTSD, who were victims of a coal mine flood disaster, and 20 individuals in a control group without a history of trauma. Notably, no significant differences in symptom severity were found within both groups (subjects with and without recent onset PTSD). The identified PTSD patients had never received any psychiatric treatment for their condition. In addition, none of the participants had ever been treated with medications for mental health issues or struggled with substance abuse, including alcohol, smoking, or drug use, in the past. Concerning the control group, no individuals fulfilled the diagnostic criteria for major depression, schizophrenia, or bipolar disorder. All the participants were right-handed males.

According to the research, those with recent onset PTSD showed more significant gray matter loss compared to the control group in several brain regions. The study found that the GMV in the left dorsal anterior cingulate cortex was lower in individuals with recent onset PTSD compared to normal controls (Figure 1, Table 1). On the other hand, individuals without PTSD had smaller GMV in the right pulvinar and left pallidum when compared to normal controls (Figure 2, Table 1). Additionally, a negative correlation was found between the CAPS scores and GMV in various brain regions of trauma survivors (both non-PTSD and PTSD), including the right frontal lobe, left anterior and middle cingulate cortex, bilateral cuneus cortex, and right middle occipital lobe. In individuals with recent onset PTSD, a negative correlation was observed between the GMV and CAPS scores in the bilateral superior medial frontal lobe and right anterior cingulate cortex (Chen et al., 2012).

It is important to note that the current study did not observe any atrophy in the hippocampus, parahippocampal gyrus, or insular cortex. This could be attributed to various reasons. For instance, previous studies on recent onset PTSD have had shorter trauma exposure times or different trauma types among individuals.

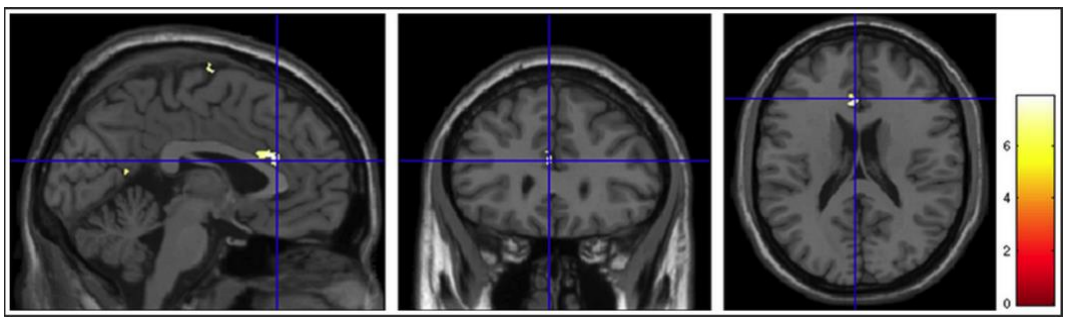


Figure 1. Regional gray matter volume reduction in recent onset PTSD compared with normal controls.

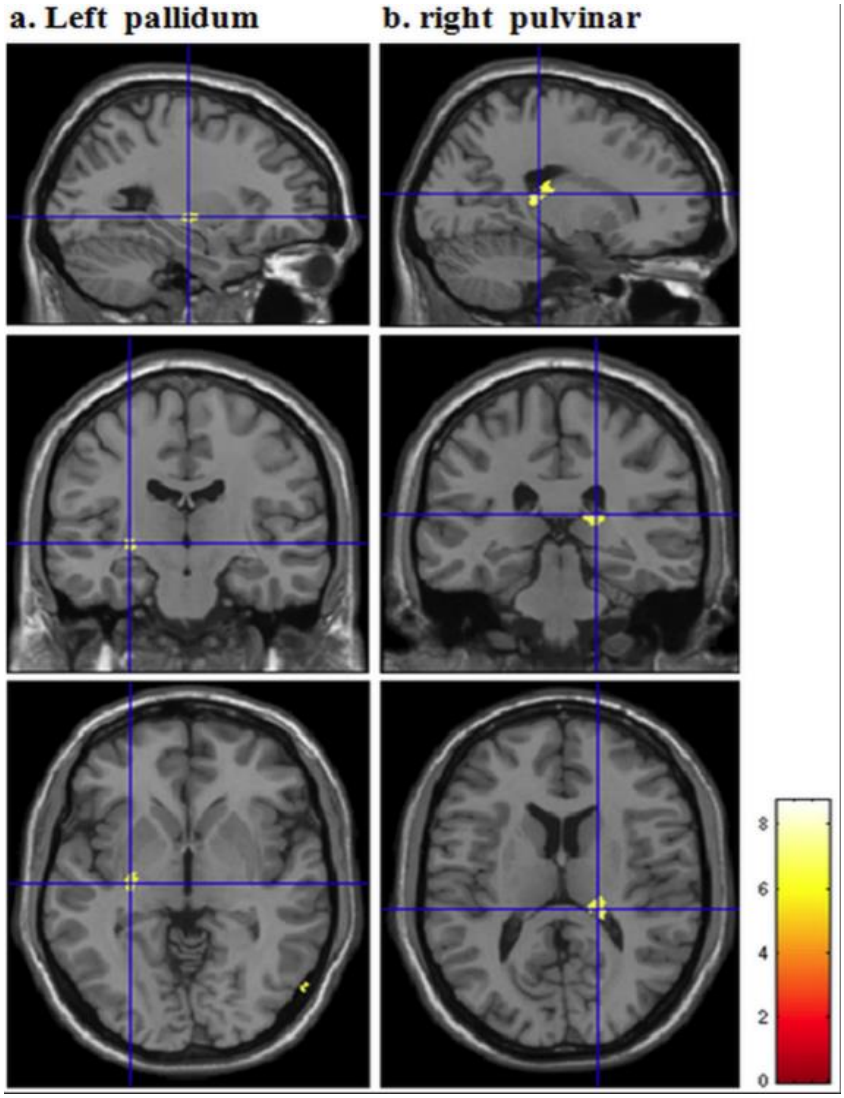


Figure 2. Regional GMV changes in trauma survivors without PTSD compared with normal controls.

The study by Jatzko et al. (2006), examined the alterations of the differences in hippocampal volumes between individuals with chronic PTSD and HC. It is important to note that this article also investigated the GMV alternation between the two groups. In terms of methodology, this study stands out as the first to employ two different approaches (VBM and manual tracing) in exploring the long-term alterations in hippocampal volumes among individuals with chronic PTSD in comparison to a control group. The chronic PTSD group included 15 patients (13 males, 2 females) who were diagnosed with chronic PTSD based on DSM IV. All patients had witnessed a tragic airplane crash at an air show, which led to their condition. The result of using a manual tracing procedure showed no differences in raw

values of total hippocampal volume, and using VBM showed no significant differences in GMV between individuals with chronic PTSD and HC.

The paper by O'Doherty et al. (2017) aimed to investigate alterations in the gray matter among individuals diagnosed with PTSD who had been exposed to civilian trauma. For this purpose, the participants were categorized into three different groups; those diagnosed with PTSD after experiencing civilian trauma, those who experienced trauma but did not develop PTSD, and healthy individuals without a history of trauma. Each group consisted of 25 people. There were no differences between the three groups in terms of age and education.

The study found significant differences in the volume of gray matter in various brain regions. The most notable differences were observed in the amygdala, hippocampus, and putamen among individuals with PTSD compared to HC. Additionally, individuals with PTSD had lower GMV in several other brain regions, including the anterior division of the bilateral cingulate gyrus, frontal pole, and paracingulate gyrus. The largest differences in gray matter were seen in the cingulate gyrus and frontal pole within frontal regions (Figure 3; Table 1) (O'Doherty et al., 2017). However, some regions, such as the cingulate gyrus, hippocampus, and frontal medial cortex, showed greater volume loss in PTSD compared to the trauma-exposed group. Additionally, the left frontal pole and right thalamus also presented larger volumes of reduction.

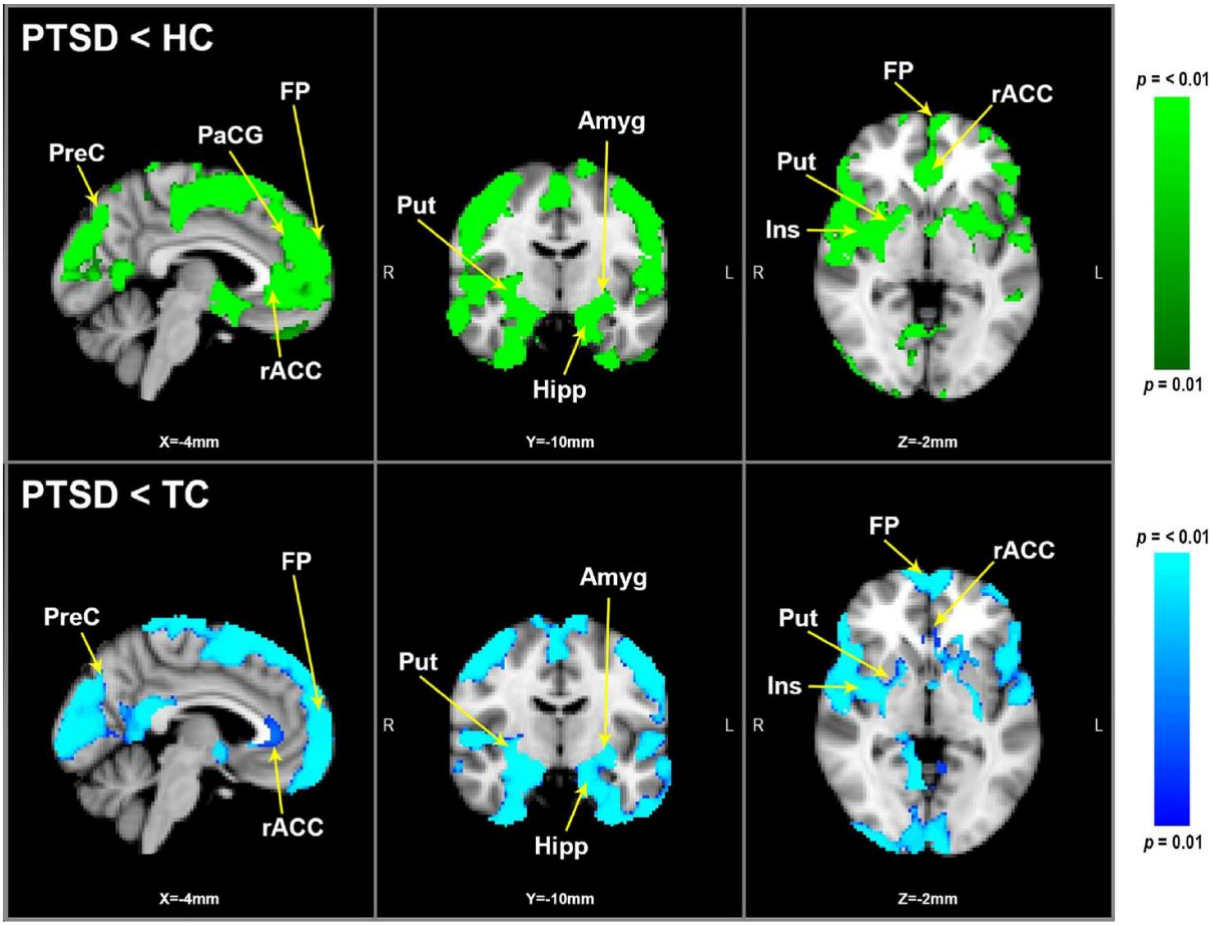


Figure 3. VBM gray matter results: group difference depicting GM reductions. Statistically significant clusters of GM changes calculated using 25 (13F/12M) PTSD subjects, 25 (13F/12M) HC and 25 (13F/12M) TC. Top panel depicts PTSD vs HC whole brain analysis; green indicates significant clusters of voxels (FWE corrected for multiple comparisons at $p < 0.01$, $k > 10$ voxels) with reduced GM volume in PTSD compared to HC. Bottom panel depicts PTSD vs TC whole brain analysis; blue indicates significant clusters of voxels (FWE corrected, $p < 0.01$, $k > 10$ voxels) with reduced GM volume in PTSD compared to TC. Abbreviations are as follows: HC = healthy controls; TC = trauma controls; GM = gray matter; Amyg = amygdala; rACC = rostral anterior cingulate cortex; FP = frontal pole; Hipp = hippocampus; Ins = insula; PaCG = paracingulate gyrus; PreC = precuneus cortex; Put = putamen; L = Left; R = Right.

In the study by Zhang et al. (2011), they examined whether regional gray matter and white matter volumes and density differ between a group of twenty recent onset PTSD patients who were stuck in a mine for 72 hours compared with a control group of ten who experienced the same trauma but did not develop PTSD. The results of Zhang et al. (2011) study revealed significantly reduced gray matter volume in the bilateral calcarine cortex, left hippocampus, left hemisphere, and right hemisphere when comparing the patients with PTSD with trauma survivors without PTSD (Figure 4, Table 1).

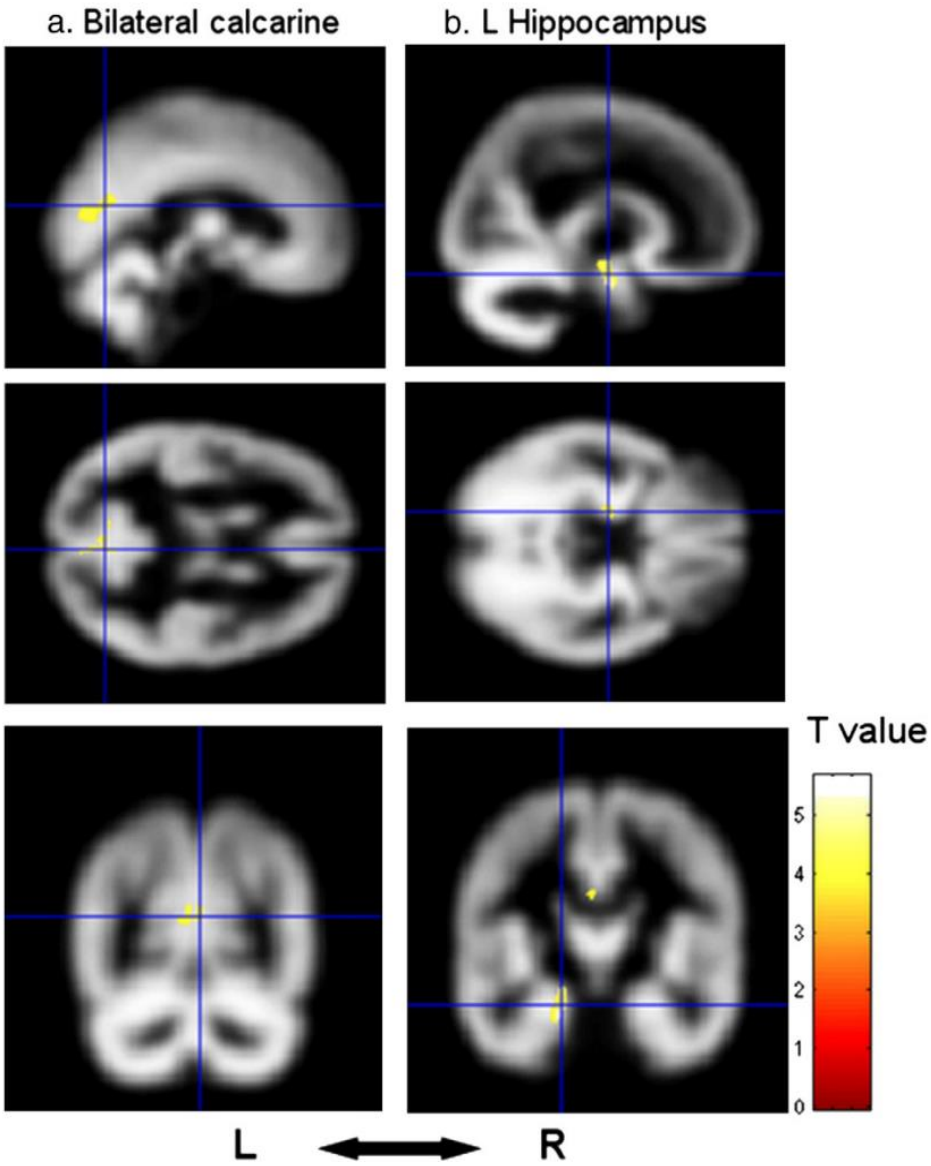


Figure 4. Regional gray matter volume decreased in recent onset PTSD patients versus trauma survivors without PTSD, as revealed by VBM. Regional gray matter volumes decreased in the following areas were rendered onto orthogonal slices of the averaged gray matter imaging of the present study subjects: (a) bilateral calcarine cortex; (b) left hippocampus. L, left hemisphere; R, right hemisphere. PTSD, post-traumatic stress disorder.

In the study by Zhang et al. (2014), they examined coal mine gas explosion survivors who developed PTSD. 24 male survivors from the disaster were recruited by Zhang and his colleagues to participate in a study about gray matter volume in the hippocampus and amygdala in individuals with PTSD compared to healthy controls. 25 individuals who were the PTSD patients' colleagues but did not experience the same disaster were enrolled as controls. They used conventional MR images to exclude visible brain lesions in both participant groups. Eight PTSD participants were then excluded because of their visible brain lesions, while all controls exhibited normal MRI appearance. Another two patients were

excluded due to them not meeting the diagnostic criteria for current PTSD. Which resulted in 14 PTSD patients being included in the final analysis (Zhang et al., 2014). The VBM results showed that PTSD patients had a decreased GMV in the bilateral hippocampi compared to controls, especially in the left hippocampus (Figure 5, Table 1).

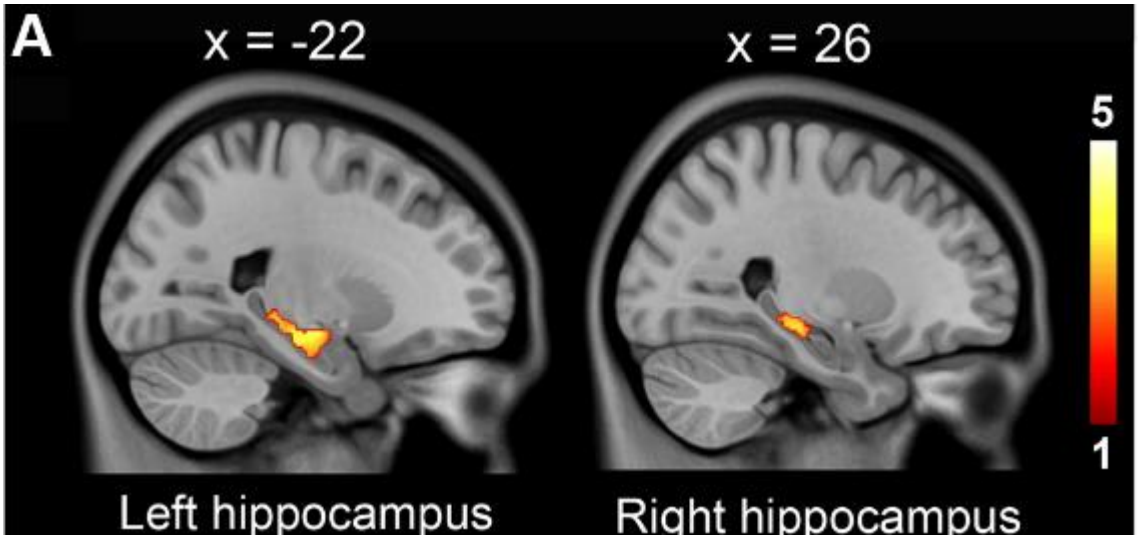


Figure 5. Reduced GMV of the bilateral hippocampus in PTSD patients compared to controls.

Tan and colleagues (Tan et al., 2013) compared the difference in brain structure between 12 mine disaster survivors with chronic PTSD, 7 cases of improved PTSD symptoms, and 14 controls who went through the same trauma but did not develop PTSD. From the beginning, the study had eighteen patients with chronic PTSD, but three cases were excluded due to their exclusion criteria and seven cases were transferred to the symptoms improved group. Moreover, another participant in the chronic PTSD group was excluded due to an imaging data error caused by head movement. Lastly, 12 cases in the PTSD patient group and 7 cases in the symptoms improved group were included in their analysis. In the TC group, there were fourteen participants (Tan et al., 2013). The results showed that the GMV was the highest in the TC group subsequent to the symptoms-improved group and lastly, the lowest GMV was detected in the chronic PTSD group. When weighed against TC, the GMV in the left superior parietal lobule and right superior frontal gyrus was reduced in the chronic PTSD group (Figure 6; Table 1) (Tan et al., 2013).

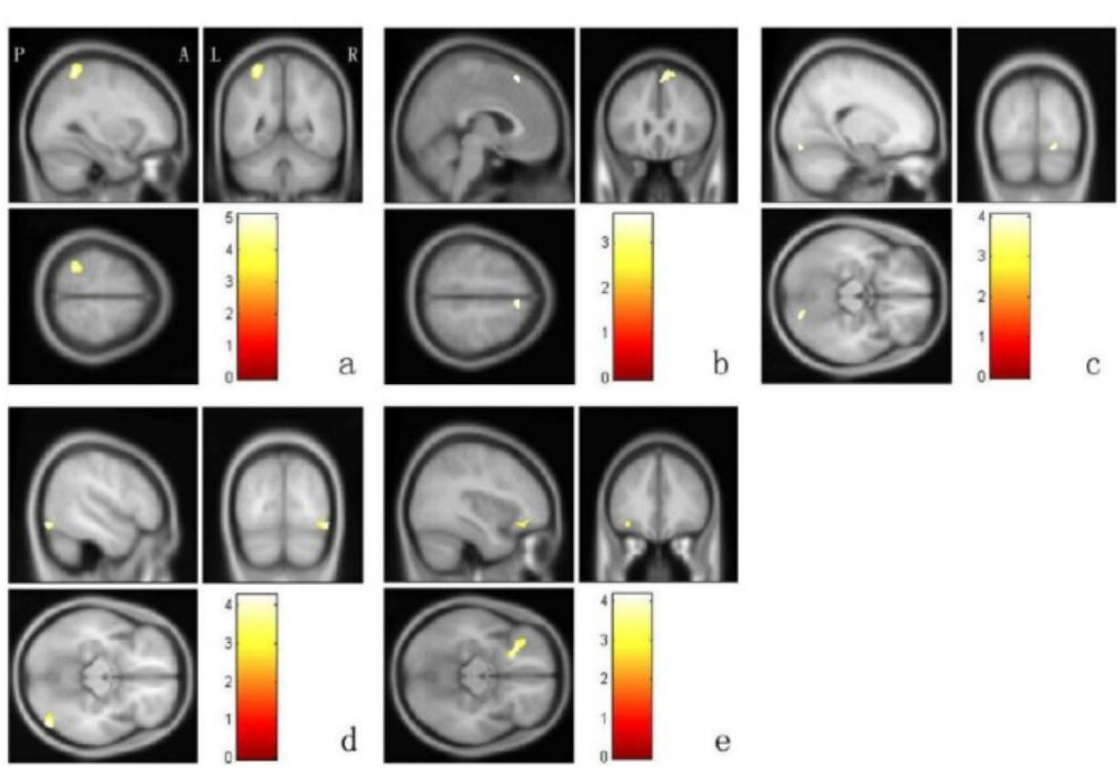


Figure 6. Comparison of gray matter volume in brain areas using VBM. (a) The left superior parietal lobule (post-traumatic stress disorder patients group < trauma control group); (b) the right superior frontal gyrus (post-traumatic stress disorder patients group < trauma control group); A: Anterior; P: posterior; L: left; R: right. The color bar in each image represents the T value, and the higher T values indicate greater differences.

Cheng et al. (2015) conducted a study with the aim of finding neuroanatomical differences between PTSD patients, obsessive-compulsive disorder (OCD) patients, and social anxiety disorder (SAD) patients compared with HC. In the PTSD group, there were 30 patients and in the HC group, there were thirty patients, hence the sample size is 60. The results they found were reduced GMV in the bilateral hypothalamus and left inferior parietal lobule (IPL) as well as in a cluster coinciding with the right middle temporal gyrus (MTG), right inferior temporal gyrus (ITG), and right fusiform gyrus in the PTSD group compared to HC (Figure 7; Table 1).

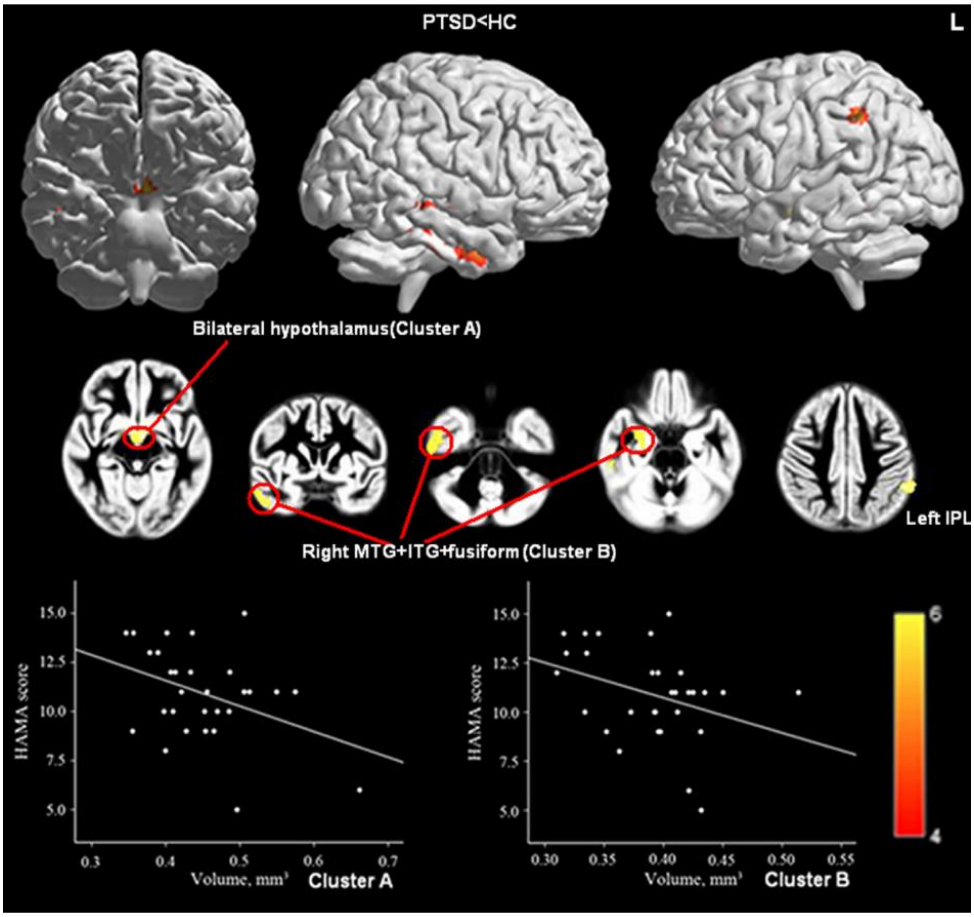


Figure 7. Significant GMV decrease in patients with PTSD compared with controls (upper panel).

Table 1.

Author	Sample Size	Comparison	Gray matter alterations
1. Cheng et al. (2015)	n= 60	30 PTSD patients and 30 HC	Reduced GMV in bilateral hypothalamus and left inferior parietal lobule (IPL) as well as in a cluster coinciding with right middle temporal gyrus (MTG), right inferior temporal gyrus (ITG), and right fusiform gyrus in the PTSD group compared to HC
2. Tan et al. (2013)	n= 33	12 patients with chronic PTSD vs 7 patients with improved PTSD vs 14 TC	Reduction of the gray matter volume in the left superior parietal lobule and the right superior frontal gyrus of PTSD patients compared with TC
3. Zhang et al. (2014)	n= 39	14 patients with PTSD and 25 TC	PTSD patients had a decreased gray matter volume (GMV) in the bilateral hippocampi compared to TC, especially in the left hippocampus
4. Zhang et al. (2011)	n= 30	20 recent onset PTSD patients and 10 TC	Decreased gray matter volume in the left hippocampus and bilateral calcarine cortex in recent onset PTSD patients compared with TC
5. Chen et al. (2012)	n= 40	10 recent onset PTSD patients and 10 TC vs 20 HC	Lower GM in the left dorsal anterior cingulate cortex was lower in individuals with recent onset PTSD and TC had smaller gray matter volume in the right pulvinar and left pallidum vs HC
6. Jatzko et al. (2006)	n= 30	15 chronic PTSD vs 15 HC	No differences in GMV
7. O'Doherty et al. (2017)	n= 75	25 with PTSD vs 25 TC and 25 HC	PTSD vs HC: Lower GM in the amygdala, hippocampus, and putamen, the anterior division of the bilateral cingulate gyrus, frontal pole, paracingulate gyrus, and frontal pole within frontal regions in PTSD group PTSD vs TC: Lower GM in cingulate gyrus, hippocampus, frontal medial cortex, the left frontal pole, and right thalamus in PTSD group

Discussion

In the present study, we investigated the gray matter alterations in individuals with PTSD compared with controls diagnosed with PTSD via CAPS using VBM as a method. To pursue this, we examined the literature containing our inclusion criteria. Our results showed that GMV was reduced in the brain of PTSD patients compared to controls. However, the study by Jatzko et al. (2006), did not find any differences between PTSD patients and controls.

One area that seemed to be frequently shown was the hippocampus, amygdala, and hypothalamus. As mentioned in the introduction, there are certain areas that are known to be associated with PTSD according to previous research. Some of these areas are the hippocampus, amygdala as well as cortical regions including the anterior cingulate, insula, and orbitofrontal region, which all play their part in interconnecting to form a neural circuit that among other functions mediates adaptation to stress and fear conditioning (Sherin & Nemeroff., 2011). In this systematic review, we have declared that several studies support that proposition by discovering reduced GMV in these areas.

Limitations

There are several limitations that should be taken into consideration in this study. The sample sizes in the studies included ranged from 30 to 75. According to Pell et al. (2008), the ideal number of subjects to detect volume loss in the hippocampus and thalamus through VBM analysis is between 70 - 90 participants. Since several of our studies examined the hippocampus and thalamus with a sample size under 70 it should be noted that their sample sizes are not ideal. Furthermore, the majority of participants were males. Although due to research by Bremner et al. (1997), they did not find a gender effect on hippocampus volume in their study, it would still be better to include both female and male participants in the PTSD and control groups.

Another point to consider as a limitation is that the control groups in the studies differed. Some of them were trauma-exposed controls and some of them were healthy controls. One limitation that Zhang et al. (2011) mentioned in their study was that they particularly focused on trauma-exposed individuals without including a control group consisting of non-trauma-exposed individuals. Having a healthy control group included as well would make it possible to compare the results of PTSD patients, trauma-exposed individuals, and healthy controls. This is something that could be applicable to all the articles we included that did not consist of a healthy control group.

As well, one study exclusively examined the effect of PTSD on the hippocampus (Jatzko et al., 2006) and as mentioned previously, they did not find any differences between PTSD patients and controls. However, eight participants in the study by Jatzko et al. (2006) had used serotonin reuptake inhibitors (SSRI) as medication for a brief period in the past. Although the participants had not used SSRI regularly, it should be noted that the use of SSRI has, according to some studies, reversed hippocampal atrophy and functional deficits to a significant degree (Sherin & Nemeroff., 2011). To exclude that this happened to the participants in the study by Jatzko et al. (2006) more information about how long they used SSRI and how it affected them is needed. Other limitations to their study are their small sample size, a large age range, and finally, some subjects with PTSD had either received psychosocial treatment in the past or were currently undergoing it; which might lead to a deceleration or reversal of the atrophy of gray matter (Jatzko et al., 2006).

Additionally, Zhang et al. (2014) investigated the amygdala and hippocampus of coal mine gas explosion survivors, which is the same participant group that Tan et al. 2013 examined, however, it is not disclosed if it is exactly the same participants. A limitation mentioned by Zhang and colleagues is the possible subtle brain damage that being exposed to a coal mine gas explosion might have caused, however, patients with visible brain lesions

were excluded. Although, this does not rule out the fact that poisoning from the explosion could cause subtle damage to the brain that could affect the results of the study.

The study by O'Doherty et al. (2017) contained several limitations. They mention that the application of VBM perhaps was not a practical method in their study due to the probability of inducing artificial volumetric differences and failing to detect changes in GMV in the amygdala and subfield of the hippocampus; another limitation was, discrepancies in education levels between the trauma survivors and normal controls as well as belonging to the different community, could have influenced the results of the study. However, Pell et al. (2008) claim that in a control group size of 70-90, it does not matter if the control groups are matched or not, since the matched control group did not demonstrate greater superiority to deliberately "unmatched" groups. Nevertheless, the study by O'Doherty only consisted of 25 controls, which means that it might not be applicable to the theory by Pell et al. (2008).

Social and ethical issues

There are some social and ethical issues to consider in this systematic review, and when conducting studies on patients with PTSD. The vulnerability of patients with PTSD needs to be considered. Privacy and confidentiality are important factors as well and are as prominent in research on PTSD patients as in any other study. PTSD is a sensitive mental health condition, and patients may hesitate to share their experiences with researchers.

In addition, the recruitment of participants with PTSD may be difficult due to the stigma surrounding the condition, leading to sampling bias. Furthermore, not everyone may have access to care even though they fulfill symptoms of PTSD. Sampling bias may limit the generalizability of the results of the study. However, when conducting research on PTSD and its neural correlates, it can also contribute to lowering the stigma and hopefully lead to a discussion in society. Addressing these social and ethical issues is critical to ensure that studies on PTSD patients are conducted in a responsible and ethical manner, to protect the rights and integrity of the participants.

The other significant issue could be the dissemination of findings. Researchers must make sure to report accurately and responsibly to avoid sensationalizing or misrepresenting the disorder. Dissemination of results should be communicated clearly, with potential implications for individuals with PTSD, mental health services, and public awareness taken into account.

Potential emotional distress is another important concern that needs to be considered. It is crucial for researchers to handle interviews, assessments, or interventions with sensitivity to minimize any harm. It is important to have appropriate measures in place, such as providing breaks, emotional support, or follow-up care, to address any distress that may arise during or after the study.

Final conclusions

The current review aimed to identify studies that investigated differences in GMV in subjects with PTSD compared to a control group. Due to our inclusion criteria, we selected seven studies. Six out of seven studies demonstrated alterations in GMV in various parts of the brain between individuals with PTSD and those in the control group.

Altogether, our review has demonstrated that there are GMV alterations between individuals with PTSD and those without. However, due to the study's restrictions, more research is needed to make our conclusion applicable globally.

In conducting future research on the relationship between GMV and PTSD, there are several key considerations that researchers should keep in mind. These include recruiting a sample that accurately represents the population of interest and striving for diversity in terms of trauma type and severity, age, and comorbidities. Additionally, researchers should explore more advanced and precise techniques beyond VBM to provide more accurate and additional insights into GMV reduction. In future research, it would also be interesting to examine whether the GMV in PTSD patients and TC significantly differs from HC in the studies that did not include HC. Furthermore, since several studies used TC and not HC, it would be interesting to examine what led to these individuals not developing PTSD even though exposed to the same trauma. Are there some underlying brain areas involved here, or genetic advantages influencing this?

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