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## Post-traumatic stress symptoms correlate with smaller subgenual cingulate, caudate, and insula volumes in unmedicated combat veterans

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### Abstract

Prior studies have examined differences in brain volume between PTSD and control subjects. Convergent findings include smaller hippocampus and medial prefrontal cortex volumes in PTSD. However, post-traumatic stress symptoms (PTSS) exist on a spectrum, and neural changes may occur beyond the diagnostic threshold of PTSD. We examined the relationship between PTSS and gray matter among combat-exposed U.S. military veterans. Structural brain MRI was obtained on 28 combat veterans from Operations Enduring and Iraqi Freedom. PTSS were assessed using the Clinician-Administered PTSD Scale (CAPS). Thirteen subjects met criteria for PTSD. Subjects were unmedicated, and free of major comorbid psychiatric disorders. Images were analyzed using voxel-based morphometry, and regressed against the total CAPS score and trauma load. Images were subsequently analyzed by diagnosis of PTSD vs. non-PTSD. CAPS scores were inversely correlated with subgenual cingulate (sgACC), caudate, hypothalamus, insula, and left middle temporal gyrus (MTG). Group contrast revealed smaller sgACC, caudate, hypothalamus, left insula, left MTG, and right MFG in the PTSD group. PTSS are associated with abnormalities in limbic structures that may underlie the pathophysiology of PTSD. These abnormalities exist on a continuum with PTSS, beyond a diagnosis of PTSD.

### Keywords

neuroimaging; anxiety; circuitry; trauma; PTSD

### 1. Introduction

Post-traumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) are highly prevalent in military service members returning from Operations Enduring/Iraqi Freedom (OEF/OIF) (Hoge et al., 2006). As many as 30% of returning veterans have been found to

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have PTSD or significant PTSS one year post-deployment (Thomas et al., 2010). There is a great need to better understand the pathophysiology of PTSD and discover biomarkers of the illness. This knowledge could eventually aid in the detection of vulnerability (or resilience) prior to, or shortly after, trauma exposure, or be used as an additional assessment for illness severity in PTSD.

One approach of elucidating the pathophysiology of PTSD has been the use of structural brain MRI, with comparison between PTSD and control groups. Convergent findings include smaller hippocampus and medial prefrontal cortex (mPFC) volumes, including the anterior cingulate cortex (ACC). Several studies also suggest reduced insula volumes in PTSD (Corbo et al., 2005; Chen et al., 2006; Kasai et al., 2008). The hippocampus is important for new memory consolidation, processing of contextual emotional memory, and inhibitory feedback on the HPA axis (Leuner and Gould, 2010). The mPFC plays important roles in emotion regulation and internal expression of emotion/fear conditioning (Phillips et al., 2008). The ventromedial (vm)PFC in particular supports fear extinction recall (Quirk et al., 2006).

Studies of subjects with PTSD suggest both overgeneralized fear responses and impaired fear extinction (e.g. (Peri et al., 2000; Orr et al., 2000; Jovanovic et al., 2010)). Functional brain studies have documented increased amygdala activation to a variety of emotional stimuli (Shin and Liberzon, 2010), and studies of fear extinction have revealed decreased activation of the vmPFC and hippocampus (e.g. (Milad et al., 2009; Bremner et al., 2005)). The above findings, along with structural brain studies, have led to a working model of PTSD in which the amygdala shows enhanced activation to emotional stimuli, with impaired recruitment of the vmPFC and hippocampus in modulating and extinguishing fear responses.

However, some studies have found no differences in these brain structures in PTSD subjects compared to trauma-exposed or healthy controls (for review of structural brain studies in PTSD, see (Shin and Liberzon, 2010)). These null findings may reflect variation in patient populations, trauma types, magnetic resonance imaging (MRI) acquisition parameters, morphometric analysis (e.g., manual tracing vs. automated algorithms), medication exposure, and relatively small effect sizes for some brain regions (Karl et al., 2006).

Another possibility for inconsistency in the literature is the variability in PTSD symptom severity across studies, e.g. (Fennema-Notestine et al., 2002; Gilbertson et al., 2002; Apfel et al., 2011). However, PTSS exist on a spectrum, and different thresholds of defining PTSD could lead to different findings. One potential solution to this is the use of a dimensional symptom approach, in particular by examining the neural correlates of PTSS across all trauma-exposed individuals (below and above the PTSD threshold). The study of PTSS is in line with the shift towards the dimensional assessment of symptoms and psychopathology being proposed in DSM-5 (Helzer and American Psychiatric Association, 2008). Dimensional analyses may also indicate greater specificity of neural changes to PTSS (and thus PTSD).

Several studies have identified correlations between regional brain volumes and PTSD symptom severity within the PTSD group only. For example, ACC volume (Woodward et al., 2006; Yamasue et al., 2003) and hippocampal volume (Gilbertson et al., 2002; Bremner et al., 2003; Villarreal et al., 2002) have been inversely correlated with PTSD severity in subjects with a diagnosis of PTSD. A meta-analysis found that reductions in hippocampal volume were more likely to manifest in subjects with severe PTSD when compared to subjects with moderate PTSD and controls (Karl et al., 2006). To our knowledge, no prior studies have examined the correlation of PTSS and gray matter volume in trauma-exposed individuals both with and without a diagnosis of PTSD.

To this end, this study aims to complement previous morphometric studies of PTSD by examining the relationship between PTSS and regional brain volumes in combat-exposed OEF/OIF military veterans, with subthreshold and threshold PTSD. We hypothesized that greater PTSS would be associated with smaller volumes in the ACC, hippocampus, and insula. However, smaller regional brain volumes could be a result of trauma exposure itself (and not simply PTSS). For example, smaller hippocampal volume has been associated with both trauma exposure and PTSD (Woon et al., 2010). Furthermore, childhood and adult trauma may have differential impacts on brain volume (Lupien et al., 2009). For example, the hippocampus appears particularly sensitive to childhood trauma (Andersen et al., 2008), whereas the ACC remains sensitive into adulthood (e.g. (Kasai et al., 2008)). We therefore included self-reported childhood and adult trauma exposure with PTSS in the same model. Finally, we conducted a group contrast to evaluate potential differences in brain volume in veterans with and without PTSD in order to facilitate comparison with the dimensional approach.

## 2. Methods

### 2.1. Subjects

Twenty-eight combat-exposed OEF/OIF veterans (25 males, 3 females; mean age 29.6) were recruited from the Pittsburgh area through public media advertisements. DD Form 214 documentation of prior military service was obtained from all potential participants. Subjects were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., November 2002). Past month PTSS were assessed using the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). Thirteen subjects met full criteria for PTSD as identified by the CAPS, using the F1/I2 criteria (Weathers et al., 2001). Subjects were unmedicated, and free of major comorbid psychiatric disorders as determined by the SCID. Depressive symptom severity was measured using the Beck Depression Inventory (BDI) (Beck et al., 1961). Level of combat exposure was measured with the Combat Exposure Scale (CES) (Keane et al., 1989). Participants completed the Trauma History Questionnaire (THQ) which is a self-report measure for exposure to a wide variety of traumas. It includes the number of times an event occurred and age at the time of exposure (Green, 1996). The number of trauma types experienced (i.e. number of THQ questions positively endorsed), before and after age 18 were summed to indicate childhood and adult trauma load, respectively.

Exclusion criteria for the study were: history of traumatic brain injury or neurological disease, current (past month) alcohol or illicit substance abuse or dependence, use of greater than 14 alcoholic drinks per week over the past month and confirmed on prospective diaries, and failure to meet screening criteria for MRI, including the presence of metal clips, heart pacemakers, claustrophobia and possibility of pregnancy for women of child-bearing age. Written informed consent was obtained from all participants after procedures were explained according to University of Pittsburgh Institutional Review Board guidelines.

### 2.2. MRI acquisition

MRI structural brain images were acquired using a 3.0 Tesla Siemens Trio MRI scanner (Siemens, Malvern, PA) at the University of Pittsburgh Magnetic Resonance Research Center. Three-dimensional sagittal high-resolution MPRAGE scans were acquired with the following parameters: TE: 2.98ms, TR: 2300ms, slice thickness: 1.2mm, 160 slices, flip angle: 9°, FOV: 256×240mm, inversion time (IT): 900 ms and image matrix 256 by 240 that covered the entire brain.

### 2.3. Image preprocessing and VBM

Image processing and voxel based morphometry (VBM) were performed with Statistical Parametric Mapping, Version 8 (SPM8, Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>), that was executed in Matlab 7.2 (Mathworks, Sherborn, MA). DICOM files were converted to NIFTI-1 format (<http://nifti.nih.gov>). As per our prior work (Almeida et al., 2009), converted files were segmented into gray and white matter, and normalized to standard international consortium for brain mapping template using a unified model integrated within SPM8. Standard SPM values were selected to bias regularization (0.0001) and FWHM cutoff (60 mm). Voxel values were modulated by the Jacobian determinants derived from the spatial normalization; brain structures that had volumes reduced after spatial normalization thereby had total counts decreased by an amount proportional to the degree of volume discounted. The final voxel resolution after normalization was 2×2×2 mm. Images were smoothed with a 12-mm Gaussian kernel. For analysis of the hippocampus only, images were smoothed with a 4-mm Gaussian kernel as suggested by prior studies (Kasai et al., 2008; Maguire et al., 2000).

### 2.4. Statistical analysis

Processed gray matter images were analyzed in a multiple regression model within SPM8 to test our primary hypothesis, that greater PTSS would be associated with smaller gray matter in the ACC, hippocampus, and insula. Regressors included the total (past month) CAPS score, childhood trauma load, and adult trauma load. All images were covaried for total gray matter volume (GMV) as determined by Easy Volume (Cyril Pernet, [http://www.sbirc.ed.ac.uk/cyril/cp\\_download.html](http://www.sbirc.ed.ac.uk/cyril/cp_download.html)). Given the significant findings with regression against the total CAPS score (see below), secondary analyses were conducted within SPSS (version 18) on extracted cluster averages that were adjusted for total GMV. First, current depression scores from the BDI and age were added as additional regressors to examine whether these variables accounted for part of the correlation between CAPS-measured PTSS severity and GMV. Second, normalized cluster averages were entered into a multivariate regression with CAPS symptom subscores (B: re-experiencing, C: avoidance/numbing, and D: hyperarousal) to identify whether specific categories of PTSD symptoms were associated with smaller regional brain volumes observed with total CAPS scores. Finally, a voxel-wise group contrast was conducted within SPM8 by dividing subjects into diagnostic groups of PTSD ( $n=13$ ) and non-PTSD ( $n=15$ ), with total GMV as a covariate, to compare methods of contrast (i.e. dimensional vs. group contrast). Regional GMV findings were considered significant for uncorrected  $P<0.001$  at the voxel level with a minimum spatial extent of 50 contiguous voxels. For Pearson/Spearman correlations and t-tests in SPSS, results were considered significant at  $P<0.05$ , two-tailed. For additional multivariate regressions of extracted cluster values associated with total CAPS score, Bonferroni correction was applied based on the number of clusters examined ( $P<0.05/4$  or 0.013).

## 3. Results

### 3.1. Demographics and psychometrics

Means and standard deviations are shown in Table 1 for age, total CAPS score, combat exposure, BDI score, and number of childhood and adult trauma types. One subject also met criteria for generalized anxiety disorder in the past month. No other concurrent psychiatric illnesses were identified. Past DSM-IV diagnoses are listed in Table 1. Correlational analysis revealed that CAPS score was significantly associated with the BDI ( $r=0.84$ ,  $P<0.001$ ) and adult trauma load ( $r=0.46$ ,  $P=0.015$ ). Adult trauma load was correlated with the BDI ( $r=0.43$ ,  $P=0.021$ ), CES ( $r=0.38$ ,  $P=0.046$ ), and childhood trauma load ( $r=0.46$ ,  $P=0.013$ ). Comparison of clinical variables between the diagnostic groups revealed that the PTSD group had significantly greater total CAPS scores ( $t_{26}=6.2$ ,  $P<0.001$ ), BDI ( $t_{26}=3.7$ ,

$P < 0.01$ ), and adult trauma load ( $t_{26} = -2.1$ ,  $P < 0.05$ ) relative to the non-PTSD group (Table 1). The groups did not differ on other variables.

### 3.2. Gray matter volume

Whole brain regression in SPM8 revealed that CAPS score was inversely correlated with gray matter in a large cluster comprising the subgenual anterior cingulate cortex (sgACC, BA25), caudate nucleus, and hypothalamus (Table 2, Figure 1). CAPS score was also inversely correlated with left and right anterior insula (BA13) (Figure 2), and left middle temporal gyrus (MTG, BA21) (Table 2, Supplemental Figure 1). Childhood trauma load was inversely correlated with the left inferior parietal cortex (BA2), and cerebellum (Table 2, Supplemental Figure 2). No significant correlations were observed between adult trauma load and regional brain volume. There were no significant correlations with any of the above variables and hippocampal volume.

### 3.3. Secondary analyses

#### 3.3.1. Covariation for combat exposure, depressive symptoms, and age—

When CES scores, BDI scores, and age were added as additional regressors against extracted average cluster values within SPSS, findings remained unchanged. CAPS score remained inversely correlated with gray matter in the sgACC cluster ( $\beta = -0.75$ ,  $P = 0.004$ ), left insula ( $\beta = -0.68$ ,  $P = 0.004$ ), right insula ( $\beta = -0.83$ ,  $P = 0.002$ ), and left MTG ( $\beta = -0.68$ ,  $P = 0.007$ ). CES and BDI scores were not significantly correlated with GMV in the above areas. Age was moderately inversely correlated with the left insula cluster ( $\beta = -0.35$ ,  $P = 0.027$ ), but showed no correlation with GMV in the other extracted regions.

#### 3.3.2. Correlations with CAPS subscores—

Multivariate regression of CAPS subscores and extracted average cluster values revealed that avoidance/numbing scores (C criteria) primarily accounted for reduced gray matter in the sgACC cluster ( $\beta = -0.64$ ,  $P = 0.008$ ), left insula ( $\beta = -0.70$ ,  $P = 0.003$ ), and right insula ( $\beta = -0.68$ ,  $P = 0.003$ ). Avoidance/numbing scores showed a trend for smaller left MTG ( $\beta = -0.38$ ,  $P = 0.087$ ). Re-experiencing (B criteria) and hyperarousal (D criteria) scores were not significantly associated with regional GMV.

**3.3.3. Group contrast—**In order to compare methods of contrast (dimensional/regression compared to group contrasts), subjects were categorized by diagnosis of PTSD vs. non-PTSD. Contrast between these two groups was largely consistent with the regression analysis. Relative to the non-PTSD group, the PTSD group showed reduced gray matter in the same large cluster comprising the sgACC, caudate, and hypothalamus (Figure 3A, 3B). The PTSD group showed reduced gray matter in the left, but not right, insula (Figure 3C, 3D), left MTG (BA21), and right MFG (BA10) (Table 2). Relative reductions in GMV in the PTSD group were: sgACC cluster 6.3%, left insula 10.1%, left MTG 6.6%, and right MFG 11.8%. Similar to the regression analysis, there was no significant difference in hippocampal volumes between the PTSD and non-PTSD groups.

## 4. Discussion

To our knowledge, this is the first reported study to examine the correlation of PTSS and regional gray matter in trauma-exposed individuals both with and without PTSD. PTSS were inversely correlated with gray matter in the sgACC, caudate, hypothalamus, anterior insula, and left MTG. The caudate, sgACC, and anterior insula in particular may underlie the pathophysiology of PTSD as discussed in more detail below, and are consistent with working theoretical models of brain pathophysiology in PTSD (Shin and Liberzon, 2010). Furthermore, there was no significant correlation between these brain regions and childhood

or adult trauma load. Together, this suggests specificity of these brain changes with PTSS, and that they are not simply due to depressive symptoms or trauma exposure itself.

When contrasted by diagnosis (PTSD and non-PTSD), smaller volumes were observed in the sgACC, caudate, left (but not right) insula, left MTG, and right MFG in the PTSD group, largely similar to the regression analysis. The size of these gray matter reductions (6–12%) is similar to differences observed in studies of individuals with major depression (Koolschijn et al., 2009). The consistency of findings using these two methods suggests the utility of whole brain correlation with symptom dimensions beyond diagnostic groups. The dimensional analysis, however, suggests that these neural changes are specific to PTSS and likely occur even below the diagnostic threshold of PTSD. This approach could be useful to complement standard group contrasts and is in line with the dimensional approaches proposed for DSM-5 and the proposed NIMH Research Domain Criteria (RDoC, with particular relevance for the fear/extinction domain) (Helzer and American Psychiatric Association, 2008; Insel et al., 2010).

Our study revealed that PTSS correlated with smaller caudate volume. The caudate nucleus, part of the striatum, is heavily involved in reward anticipation and response. Abnormal functioning within this structure has been documented in depression (Eshel and Roiser, 2010), substance abuse (Volkow et al., 2011), and PTSD, e.g. (Elman et al., 2009; Vythilingam et al., 2009; Sailer et al., 2008). Impaired recruitment of the striatum may in part mediate the anhedonia that is characteristic of depression, addictive disorders, and PTSD. Indeed, deep brain stimulation of the striatum has been found to alleviate symptoms of depression, including anhedonia (Malone et al., 2009; Schlaepfer et al., 2008). In depression, lower caudate volume has been associated with anhedonia and greater depression severity (Pizzagalli et al., 2009). Together, these findings suggest disruption of the reward processing system may represent a common underlying impairment in PTSD, depression, and substance abuse, and may in part explain the high comorbidity of these illnesses.

PTSS also correlated with smaller ACC volume. The ACC is a heterogeneous structure supporting different functions. While the dorsal ACC supports executive/cognitive processing and voluntary control of emotion regulation, the rostral ACC supports automatic emotion regulation, conflict monitoring, and attentional control of emotional stimuli. Both of these areas appear to support the expression of fear, pain, and emotion in humans (Phillips et al., 2008). The sgACC in particular shows homology to the infralimbic cortex in rats and plays a prominent role in visceromotor regulation and extinction of fear memory (Phillips et al., 2008; Quirk et al., 2006). Abnormalities in the medial prefrontal cortex (mPFC), including the sgACC, have been documented in PTSD in both structural and functional neuroimaging studies. Structural findings include reduced volumes of the orbitofrontal cortex (Thomaes et al., 2010), ACC (rostral and dorsal) (Woodward et al., 2006), rostral ACC (Rauch et al., 2003), dorsal ACC (Chen et al., 2006; Yamasue et al., 2003; Thomaes et al., 2010; Kitayama et al., 2006), and sgACC (Rauch et al., 2003). Furthermore, prior research suggests that lower ACC volume may be an acquired change following exposure to stressful life events (Papagni et al., 2011) and the development of PTSD (Kasai et al., 2008). A number of studies (but not all) have also demonstrated reduced activation of the mPFC in PTSD (for review see (Shin and Liberzon, 2010)). These findings have led to a working model of PTSD in which amygdala activation to emotional stimuli is thought to proceed relatively unchecked by mPFC, particularly the vmPFC, which has more direct connections to the amygdala, e.g. (Ghashghaei et al., 2007). In an fMRI study, re-experiencing and avoidance symptoms were inversely correlated with ACC activation (Hopper et al., 2007), and fear extinction paradigms show impaired recruitment of the vmPFC (Milad et al., 2009; Bremner et al., 2005; Rougemont-Bucking et al., 2011). These

studies suggest impairments in fear extinction and inhibitory control of the amygdala that are mediated, at least in part, by the vmPFC. The correlation of PTSS with lower sgACC volume in the current study would be consistent with this model. The specific correlation of avoidance/numbing symptoms is somewhat more difficult to reconcile with this model, though could reflect engagement of compensatory mechanisms (and therefore circuitry) given the impairment in fear extinction that would normally have occurred via the sgACC.

Finally, PTSS correlated with lower bilateral anterior insula volume, though only the left insula was significantly different in the group contrast. The anterior insula is an important part of the limbic circuitry which is involved in the representation of interoceptive, emotional states (Critchley, 2005). Three prior studies, to our knowledge, have also documented reduced insula volumes in PTSD (Corbo et al., 2005; Chen et al., 2006; Kasai et al., 2008). Functional neuroimaging studies have, however, shown greater insula activation in response to emotional stimuli, which appears to be a commonality in multiple anxiety disorders and normal fear conditioning (Etkin and Wager, 2007). A recent study also demonstrated increased insula activity as a result of combat exposure itself, even in the absence of PTSD (van Wingen et al., 2011). In the context of these studies, the current findings suggest that trauma exposure induces, and PTSS are correlated with, reduced insula volume but increased insula activation to emotional stimuli. One possibility may be that reductions in insula volume represent a compensatory response to prolonged, heightened insula activation. Alternatively, increased activity may reflect a compensatory response for reduced volume. The reason for the dissociation between insula volume and activity remains unclear at this time, and merits further study.

Contrary to our main hypothesis, there was no relationship between PTSS and hippocampal volume, or differences in hippocampal volume between the PTSD and non-PTSD groups. Some previous studies also failed to find hippocampal volume differences in PTSD, e.g. (Fennema-Notestine et al., 2002; Bonne et al., 2001), suggesting variability of this finding in the literature. Furthermore, PTSD duration has been associated with smaller hippocampal volumes (Apfel et al., 2011; Felmingham et al., 2009). Subjects in the current study, being more recent war veterans, will not yet have had chronicity of PTSD to the extent of veterans in prior studies, which could explain the absence of hippocampal findings in this study. As mentioned earlier, hippocampal volume reductions also appear to be more evident with severe PTSD (Karl et al., 2006). Subjects with a full diagnosis of PTSD in this study had an average CAPS score of 47.5 (a moderate level of PTSD on average) and could therefore account for the lack of hippocampal grey matter differences.

There are several limitations to the current study. First, these findings are correlational only and do not prove causation. Nevertheless, the combination of correlational and group contrast approaches, and accounting for depression, age, and trauma load, does suggest specificity of these brain changes with PTSS. Second, this is a cross sectional study which makes it difficult to assess whether smaller regional brain volumes are a preexisting vulnerability factor (trait), alterations with PTSS itself (state), or a compensatory change. More longitudinal studies will be needed to address these limitations. Third, these findings may not generalize to other populations or trauma types, given the heavily male, combat veteran sample. Fourth, findings may not generalize to individuals with more severe PTSD (e.g. CAPS>80). The relatively restricted range in CAPS scores could also account for some of the similarity between the regression and group contrasts. It is nonetheless notable that some of the findings (smaller ACC and insula) have also been documented with more severe PTSD. This suggests that such changes are present even in individuals with milder PTSS. Finally, this is a relatively small number of subjects and would merit replication with a larger sample.

While subjects were free of any current alcohol or substance abuse, this study did not have measures of cumulative, lifelong alcohol use which could affect the current results. Chronic alcoholism has been associated with reduced grey matter in the superior frontal and motor cortices, cerebellum, and hippocampus (Spampinato et al., 2005; Hedges and Woon, 2010). However, PTSS were not associated with grey matter reductions in these areas in our study, making it less likely that lifetime alcohol use would account for the observed changes. In addition, removal of the 5 subjects with a history of alcohol dependence from the VBM analysis did not change the pattern of results.

There are a number of strengths of the present study. This is one of few studies to examine brain changes in OEF/OIF combat veterans. Subjects were healthy and free of major concurrent psychiatric comorbidities including alcohol and substance abuse or dependence. Subjects were medication-free, and medication is a common potential confound in clinical studies. This study was also able to account for childhood and adult trauma load which represent important potential confounds in studies of PTSD.

In summary, the current study revealed that PTSS are correlated with reduced gray matter in the sgACC, caudate, hypothalamus, and anterior insula. The similarity of these findings with the group contrast suggests that they exist on a spectrum in trauma-exposed individuals, and are present even in subthreshold PTSD. With further study, this could eventually help to identify individuals at risk for (or resilient to) developing full PTSD following traumatic events. These regions play an important role in mediating extinction of fear memory, reward, and anxious states. As such, abnormalities in these areas may represent pathophysiological changes in PTSD, a disorder characterized by heightened and generalized fear memory, anhedonia, and anxiety, all of which may be subserved by different neural circuits.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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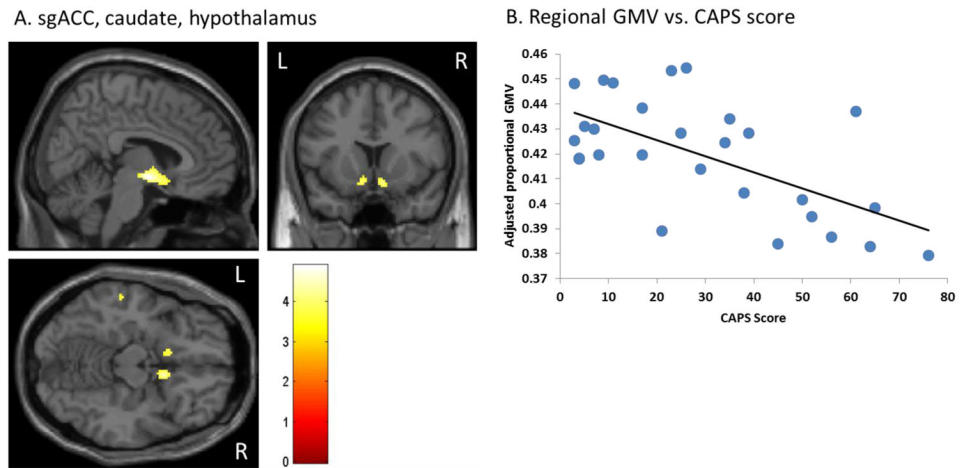
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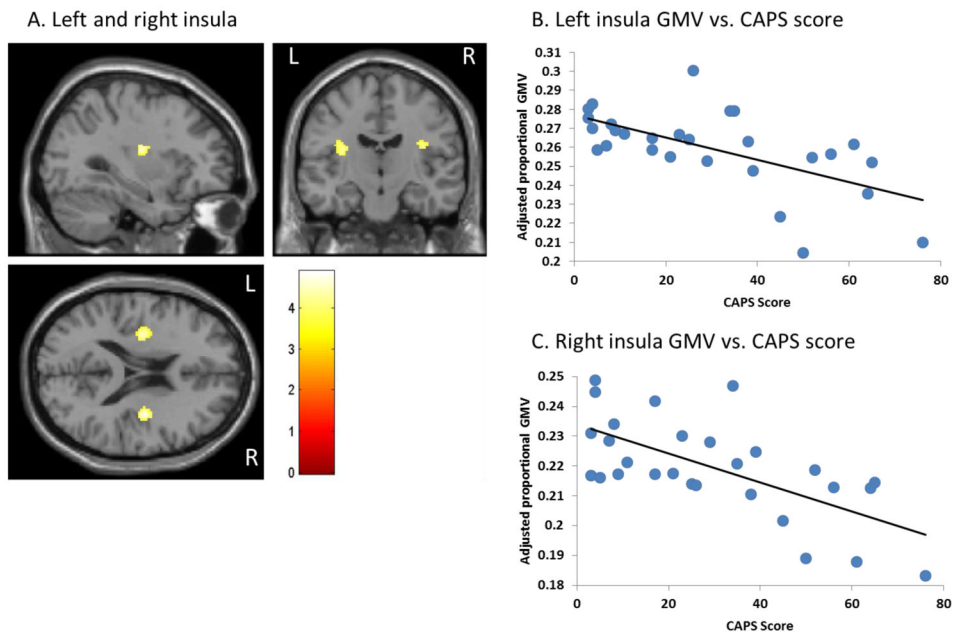
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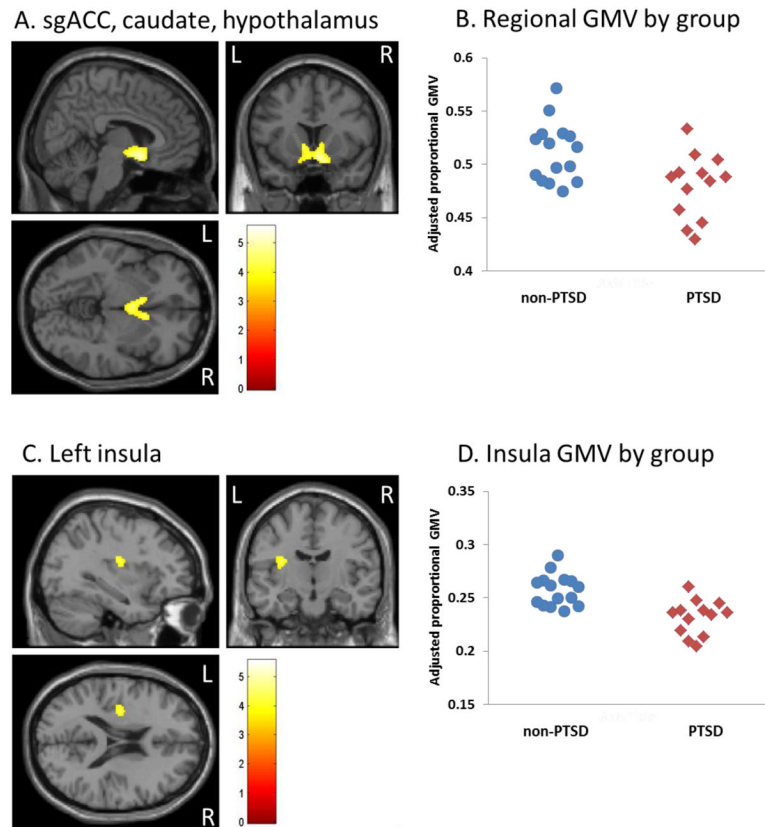
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**Figure 1.** CAPS score is inversely correlated with sgACC, caudate, and hypothalamus GMV. (A) sgACC, caudate, hypothalamus. (B) Regional GMV vs. CAPS score. Scatterplot depicts proportional GMV values averaged over all voxels in the cluster, and adjusted for total GMV. Extracted values shown here are not adjusted for depression scores or age.



**Figure 2.** CAPS score is inversely correlated with insula GMV. (A) Left and right insula. (B) Left insula GMV vs. CAPS score. (C) Right insula GMV vs. CAPS score. Scatterplots depict proportional GMV values averaged over all voxels in the cluster, and adjusted for total GMV. Extracted values shown here are not adjusted for depression scores or age.



**Figure 3.** Subjects with PTSD exhibit smaller sgACC, caudate, hypothalamus, and left insula GMV compared to non-PTSD. (A) sgACC, caudate, hypothalamus. (B) Scatterplot depicting individual sgACC/caudate/hypothalamus regional GMVs by diagnostic group. (C) Left insula. (D) Scatterplot depicting individual left insula regional GMVs by diagnostic group. Scatterplots depict proportional GMV values averaged over all voxels in the cluster, and adjusted for total GMV. Extracted values shown here are not adjusted for depression scores or age.

**Table 1**

## Demographic and clinical variables

	All Subjects	PTSD	non-PTSD
<b>n</b>	28	13	15
<b>Sex (F)</b>	3 (11%)	2 (15%)	1 (7%)
<b>Age</b>	29.6 (5.3)	28.9 (4.2)	30.1 (6.3)
<b>CAPS total</b>	29.5 (22.1)	<b>47.5 (17.5)</b>	<b>13.9 (10.9)</b>
<b>Beck Depression score</b>	5.8 (7.5)	<b>10.5 (8.9)</b>	<b>1.8 (2.0)</b>
<b>Combat Exposure Scale</b>	19.4 (10.9)	22.1 (10.0)	17 (11.4)
<b>Childhood trauma load</b>	0.9 (1.2)	0.9 (1.4)	0.8 (1.1)
<b>Adult trauma load</b>	5.9 (3.0)	<b>7.1 (2.4)</b>	<b>4.9 (3.1)</b>
<b>Past DSM-IV diagnoses</b>			
<b>Major Depressive Disorder</b>	3 (11%)	3 (23%)	0 (0%)
<b>Dysthymic Disorder</b>	1 (4%)	1 (8%)	0 (0%)
<b>Generalized Anxiety Disorder</b>	1 (4%)	1 (8%)	0 (0%)
<b>Panic Disorder</b>	1 (4%)	1 (8%)	0 (0%)
<b>Alcohol Dependence</b>	5 (18%)	4 (31%)	1 (7%)
<b>Cocaine Abuse</b>	1 (4%)	0 (0%)	1 (7%)
<b>Cannabis abuse</b>	3 (11%)	2 (15%)	1 (7%)

Values represent either count (percent) or mean (standard deviation). Values in bold are statistically different between the PTSD and non-PTSD groups, two-tailed t-test,  $P < 0.05$ . CAPS=Clinician-administered PTSD Scale (past month).

**Table 2**

Regional gray matter findings

Contrast	Region	Z-score	k	Cluster Peak Coordinates		
				x	y	z
<b>↑CAPS, ↓GMV</b>	sgACC (BA25), Caudate, Hypothalamus	4.00	352	6	-4	-8
	Left Insula (BA13)	3.87	180	-32	-12	16
	Right Insula (BA13)	3.89	111	36	-10	20
	Left Middle Temporal Gyrus (BA21)	3.78	50	-60	-26	-10
<b>↑Child Trauma, ↓GMV</b>	Left Posterior Inferior Cerebellum	3.98	429	-44	-70	-54
	Left Posterior Superior Cerebellum	3.35	108	-28	-68	-26
	Right Posterior Inferior Cerebellum	3.39	124	16	-76	-52
	Right Posterior Superior Cerebellum	3.49	58	36	-70	-26
	Left Inferior Parietal Lobe (BA2)	3.95	67	-42	-30	38
<b>non-PTSD&gt;PTSD</b>	sgACC (BA25), Caudate, Hypothalamus	4.44	813	10	8	-14
	Left Insula (BA13)	3.68	109	-32	-12	18
	Right Middle Frontal Gyrus (BA10)	4.37	92	38	42	14
	Left Middle Temporal Gyrus (BA21)	3.79	86	-64	-26	-10

Summary of smaller gray matter volume associated with greater post-traumatic stress symptoms (↑CAPS, ↓GMV), greater child trauma load (↑Child Trauma, ↓GMV), or PTSD compared to non-PTSD. Regions shown were significant at uncorrected  $P < 0.001$ , threshold  $k = 50$  voxels.  $k =$  cluster size. CAPS = Clinician-administered PTSD Scale. GMV = gray matter volume. Peak coordinates based on Montreal Neurological Institute atlas.