

**Structural Imaging Findings in PTSD:
Tracing Neuroanatomy Through the 5-Factor Model**

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Abstract

Posttraumatic stress disorder (PTSD) affects an inordinate amount of today's population. Characterized by three main types of symptoms, PTSD commonly encompasses a combination of: re-experiencing the trauma, emotional numbness and avoidance, and increased arousal. This breakdown of symptoms can be summarized as a handful of key factors. The latent structure of PTSD—focused on determining the best grouping for these symptom factors—has been widely debated. However, the 5-factor model has emerged as the best model fit. Though much has been studied about the causes and symptoms of PTSD, not only are current diagnostic measures still quite arbitrary but the neurological changes that accompany the disease have also yet to be thoroughly elucidated. In order to develop more effective and selective treatment and prevention strategies for the disorder, it is essential to adopt novel strategies to pursue neural analyses in PTSD. Here, we integrate structural brain imaging with the 5-factor PTSD diagnostic model in a population of PTSD-affected combat veterans, non-PTSD veterans, and healthy controls to discover whether certain brain structure volumes are associated with specific factors in the model. Results indicate that there are structural gray matter volume differences between PTSD and non-PTSD individuals as well as between combat veterans and healthy controls. In addition, our findings show a correlation between structural gray matter volumes and individual categories in the 5-factor model (reexperiencing and anxious arousal). These results provide a better understanding of PTSD's link to neural structures and may contribute to the development of more effective preventative, treatment, and diagnostic measures for PTSD.

Introduction

Post-traumatic stress disorder (PTSD) affects a significant proportion of the population. Currently, 1 in 5 US combat veterans suffered or are suffering from PTSD, with general population estimates for PTSD ranging from 6.4% to 6.8% (Kessler et al., 2005). PTSD is a disorder that typically develops after a terrifying ordeal involving physical harm or the threat of physical harm. Patients with PTSD frequently re-experience their traumatic events in different ways ranging from intrusive and disturbing recollections to nightmares to flashbacks and distress to physiological reactivity on exposure to reminders of the event (National Institute of Mental Health, 2014). In recent years, rapid progress in PTSD research has been achieved with functional neuroimaging studies, with the main results implicating the amygdala, medial prefrontal cortex, and hippocampus as being dysfunctional in PTSD (Hughes and Shin, 2011). However, although functional neuroimaging PTSD research has generated vast amounts of information, much is still poorly understood about the disorder (National Institute of Mental Health, 2014).

In recent years, PTSD's latent structure has been a topic of significant debate. Currently, PTSD can be evaluated through a number of different models (Armour, 2012). A novel 5-factor model—comprising five core symptom clusters: re-experiencing, avoidance, emotional numbing, dysphoric arousal (e.g., sleep difficulties), and anxious arousal (e.g., hypervigilance)—has emerged as one of the most effective for PTSD (Simms, 2002). However, DSM standards have yet to catch up with the 5-factor model. DSM-IV featured only three factors with dysphoric arousal and anxious arousal grouped together as a joint hyperarousal label and avoidance and numbing combined as a joint avoidance category. DSM-V improved upon DSM-IV by separating avoidance and numbing categories but still operates under a 4-factor model. Recognizing the differences between these three separate models is crucial for building future tools to deal with PTSD as well as to determine

the optimal model with which to pursue neural imaging analyses. As shown in a diverse range of studies, the novel 5-factor model provides a much better overall fit for PTSD symptoms than other models. Confirmatory factor analyses examining the factor structure of PTSD in three independent samples of combat veterans established that PTSD symptomatology is best represented by the 5-factor model (Pietrzak, 2012). Another study investigating PTSD symptoms in children and adolescents through 6 different factor structures concluded that the 5-factor model provided the best fit to the data (Hukkelberg, 2011). Comparison of the 3-factor, 4-factor, and 5-factor models in samples of juvenile-justice-involved adolescents also revealed that the 5-factor model fit significantly better than each of the other models (Bennett, 2014).

Significant amounts of previous research have investigated the functional neural differences exhibited in PTSD, leading to results including the hyperresponsiveness of certain structures such as the amygdala, dorsal anterior cingulate cortex and insula, the hypoactivation of the ventromedial prefrontal cortex, and abnormal/reduced response of the hippocampus (Hughes, 2011; Shin, 2004; Astur, 2006). The amygdala, hippocampus, and anterior cingulate cortex are of particular interest in PTSD research since each possesses functions that are crucial components within typical PTSD symptomatology. The amygdala is responsible for emotion processing, fear extinction, and emotion regulation; the hippocampus plays a critical role in learning, memory, and stress regulation; and the anterior cingulate cortex is involved in affect-regulation, the ability to control and manage uncomfortable emotions (Karl, 2006; Kuhn, 2012; Phelps, 2004; Stevens, 2011). However, overall, our understanding of the neurobiology of PTSD is far from complete; furthermore, there currently exist no adequate strategies to identify individuals at heightened risk for developing the disorder.

By employing structural analysis, we hope to better understand the neurobiology of PTSD, since a comprehensive grasp of the disorder is essential for the development of more effective and

selective treatment and prevention strategies. In the long run, a combination of structural and functional imaging may even reveal behavioral and neurobiological markers of the susceptibility for developing PTSD. Finally, one of structural imaging's most prominent advantages over functional imaging in the field of research is that structural imaging requires much less time, money, and effort to perform. Contingent upon the discovery of behavioral and neurobiological markers for PTSD in the future, diagnostic measures would be much more convenient and cost-effective for the health industry using structural markers and structural imaging versus functional neural markers and functional imaging (Gilaie-Dotan, 2014).

Though structural imaging in PTSD has not garnered an enormous amount of focus, a foundation of knowledge does exist. Individuals with PTSD possess certain significantly different brain structures than various controls. Maltreatment-related PTSD has been associated with adverse brain development, with PTSD children having smaller posterior cerebral and cerebellar gray matter volumes than maltreated youth without PTSD and non-maltreated participants. These gray matter volumes are inversely correlated with PTSD symptom severity (Bellis, 2015). In addition, people with PTSD typically possess smaller hippocampal volumes compared with control subjects with and without trauma exposure. Because the hippocampus is critical in learning and memory as well as stress regulation, structural alterations in the hippocampus may directly contribute to the etiology of PTSD (Burgess, 2002). However, there may be a more nuanced explanation, especially because trauma-exposed individuals without PTSD show significantly smaller bilateral hippocampi relative to non-exposed individuals. This introduces the possibility that hippocampal shrinkage is associated with trauma exposure, independent of the PTSD diagnosis (Karl, 2006). Other gray matter reductions in PTSD patients include the anterior cingulate cortex, the ventromedial prefrontal cortex, and the left temporal pole/middle temporal gyrus. Similar to the hippocampus, the amygdala has a smaller volume in PTSD individuals as well (Morey, 2012). This entire brain

structure deficit profile (which includes the hippocampus) overlaps with brain networks responsible for emotion processing, fear extinction, and emotion regulation, so it may have quite a prominent role in PTSD (Kuhn, 2012).

Currently, the diagnosis of PTSD is a highly arbitrary construct: the disorder is composed of an array of different questionnaire-determined symptoms, and, once an arbitrary threshold is crossed, we deem the individual “sick.” The 5-factor model stands as an initial step towards changing this diagnostic structure. This study builds on the 5-factor model and enables us to break this relatively subjective “PTSD versus non-PTSD” mold and shift towards a continuous inspection of symptoms rather than a rigid scheme. Structural imaging represents an incredibly promising avenue through which to objectively assess PTSD, since structural measures may be able to provide biomarkers for specific symptoms. Treatments may even need to be tailored based on each patient’s specific symptom landscape, and thus structural measures may aid in objectively mapping out these symptoms (Szabo 2015). By discovering structural correlates of each symptom cluster in the 5-factor model, we may be able to provide potential biological markers and help establish a more concrete, neurologically-based definition of PTSD.

In order to ascertain the structural correlates of each symptom cluster in the 5-factor PTSD model, we utilized structural imaging to discover whether neuroanatomical structural differences were correlated with each of the five factors as well as for overall symptom severity in the disorder. Here, we undertook a project to analyze structural imaging and the individual factors in the 5-factor model in a population of combat veterans (PTSD and non-PTSD) and healthy non-veterans to discover potential correlations between the symptom factors, overall PTSD symptom severity, and structural neural differences. Essentially, we sought to discover: do differences in brain structure correlate with the five factors and symptom severity? The healthy non-veteran group was compared

with the combat veterans to gauge the effect of experiencing trauma, separate from the effect of PTSD symptoms. Our main focus was on the analysis of the veteran population as a whole (both PTSD and non-PTSD) since our goal was to approach PTSD as a continuous spectrum of symptoms rather than as the current static “PTSD versus no PTSD” scheme.

The current study featured whole-brain voxel-based morphometry analysis focusing on gray matter volume. The analysis was broken up into two “studies.” The first study focused on group differences between our three populations while the second study focused on finding correlations between voxel densities (cortical volume thinning or thickening) and our other symptom measures (the five symptom factors and PTSD symptom severity) in order to model density as a function of these predictors. The regions we were most interested in were the ones implicated most strongly in PTSD functional imaging as well as in previous PTSD structural research: the amygdala, the hippocampus, and the anterior cingulate cortex. Based on the combination of previous functional and structural research, we predicted that these structures would be neural correlates for certain factors in the 5-factor model—more specifically, for the factors of reexperiencing, emotional numbing, and anxious arousal.

Understanding these correlations is key in progressing away from the current rigid and arbitrary PTSD diagnostic process towards a continuous inspection of symptoms, backed by the objective biological markers of structural correlates. However, though our study attempted to address these issues, we were still confronted by one of the main challenges of interpreting neural data: the uncertainty of whether structural volume differences represent a predisposition or a consequence of trauma. Previous longitudinal studies have produced preliminary results regarding the hippocampus, the anterior cingulate cortex, and the orbitofrontal cortex. Investigating soldiers before and after combat exposure, researchers discovered that decreased hippocampus volume

marks a maladaptive response to stressful military service (Admon, 2013). A separate study focused on individuals before and after the Great East Japan Earthquake. Subjects with smaller gray matter volume in the right ventral anterior cingulate cortex before the earthquake, and subjects with decreased gray matter volume in the left orbitofrontal cortex after the earthquake were more likely to have PTSD symptoms (Sekiguchi, 2013). However, these results are quite limited, and the exact associations are still uncertain. Unfortunately, the current study was inherently unable to address such questions (only a longitudinal study has the capability), but, regardless, it is important to factor in the ambiguity surrounding causal direction of trauma and structural brain volumes while analyzing this type of data.

Materials and Methods

Subjects. 79 subjects were used for this structural study (two subjects were excluded out of an initial pool of 81 because they failed to provide enough diagnostic information). Of the 79 subjects, 25 were PTSD veterans, 30 were non-PTSD veterans, and the remaining 24 were healthy non-veterans. The veterans were recruited through the VA Connecticut Healthcare System outpatient mental health clinic while the healthy controls were recruited through advertisements.

MRI Structural Acquisition. Imaging data were collected using a Siemens Trio TIM 3T scanner equipped with a 32-channel head coil, at the Yale Magnetic Resonance Research Center. High-resolution T1-weighted anatomical images ($1 \times 1 \times 1 \text{ mm}^3$) were acquired with an MPRAGE pulse sequence (TI = 900 ms, sagittal slices, 256×256 matrix) (Gilaie-Dotan, 2014).

Data Acquisition. This study drew from structural imaging data taken in an ongoing functional imaging project within the Levy Lab analyzing reversal learning in PTSD combat veterans, non-PTSD combat veterans, and control participants. Thus, the current project did not require any additional data acquisition experiments. All of the structural images and PTSD symptom scores had already been acquired by the Levy lab.

PTSD Assessment. Subjects were assessed for PTSD, corresponding symptom severity, and specific 5-factor scores through the Clinician-Administered PTSD Scale for DSM-5 (CAPS) (See Appendix A for a sample CAPS assessment sheet). The CAPS represents the gold standard for PTSD assessment and comprises 30-items in a structure interview that can be applied to make current (past month) and lifetime diagnoses of PTSD as well as assess PTSD symptoms over the past week. The questions focus on “onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and specifications for the

dissociative subtype (depersonalization and derealization)” (“Clinician-Administered PTSD Scale for DSM-5”). The severity ratings for symptoms range from 0 to 4. The CAPS score is a breakdown of the 30 item list that includes four different areas: Criteria B, C, D, and E. The 5-factor model draws on the CAPS with each of the five factors comprising a certain subset of questions within the CAPS. Before integrating both the CAPS scores and the 5-factor scores in our analysis, we converted all of these scores into z-scores to standardize the data between our subjects.

Data Analysis. Before analysis, all MRI scans were subject to a visual quality control check to ensure that no gross artifacts were present in the data. The neural data was analyzed within subject, and we performed a whole brain analysis. For both studies 1 and 2, variables associated with structural volumes at the $p < .05$ level were entered into an array of different tests. Study 1 featured multiple ANOVAs probing for group level differences between PTSD veterans and non-PTSD veterans, all veterans and healthy controls, and PTSD veterans and healthy controls. The second study utilized multiple regressions to analyze all of the structural data obtained from veteran subjects in order to determine whether gray matter volume correlated with certain factors in the 5-factor model as well as with PTSD symptom severity in general (overall CAPS scores). In both studies 1 and 2, we controlled for the effects of total intracranial volume, age, and gender. In evaluating the details for the independent variables, we conducted a post-hoc multivariable linear regression analysis, with alpha being set to .01 for these tests.

VBM Analysis. All VBM (voxel-based morphometry) analyses were performed using SPM12 to highlight gray matter volume in the subjects for the control group, the veteran group, and the PTSD-affected veteran group. The analysis involved preprocessing, second-level modeling and contrasts, and a whole-brain correction. The preprocessing featured an initial realignment of the brains and then a segmenting of the structural magnetic resonance images for each subject into gray

matter (GM) and white matter (WM) using SPM12 segmentation tools. This was followed by inter-subject registration of the GM images via the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) and then MNI normalization in SPM12 (See Appendix B for the images corresponding to each step of the preprocessing). The second level modeling and contrasts was then performed with a three level one-way ANOVA model with the PTSD veterans non-PTSD veterans, and control groups set up as dummy variables. The whole-brain correction was necessary since structural images display local variation in smoothness. Therefore, non-stationary whole-brain cluster-level correction was also applied (Gilaie-Dotan, 2014).

Results

In study 1, we focused on group-level differences in our three populations. Our first analysis, study 1A, was between PTSD veterans and non-PTSD veterans. We found a significant difference in the gray matter volume of a cluster in the left temporal region (MNI coordinates: -43.5, -4.5, -28.5, 260 mm³, $t(54) = 4.35$, $Z = 3.99$, $p(\text{uncorrected}) < 0.001$), such that non-PTSD veterans had more gray matter volume in that region in comparison to PTSD veterans (see Figure 1).

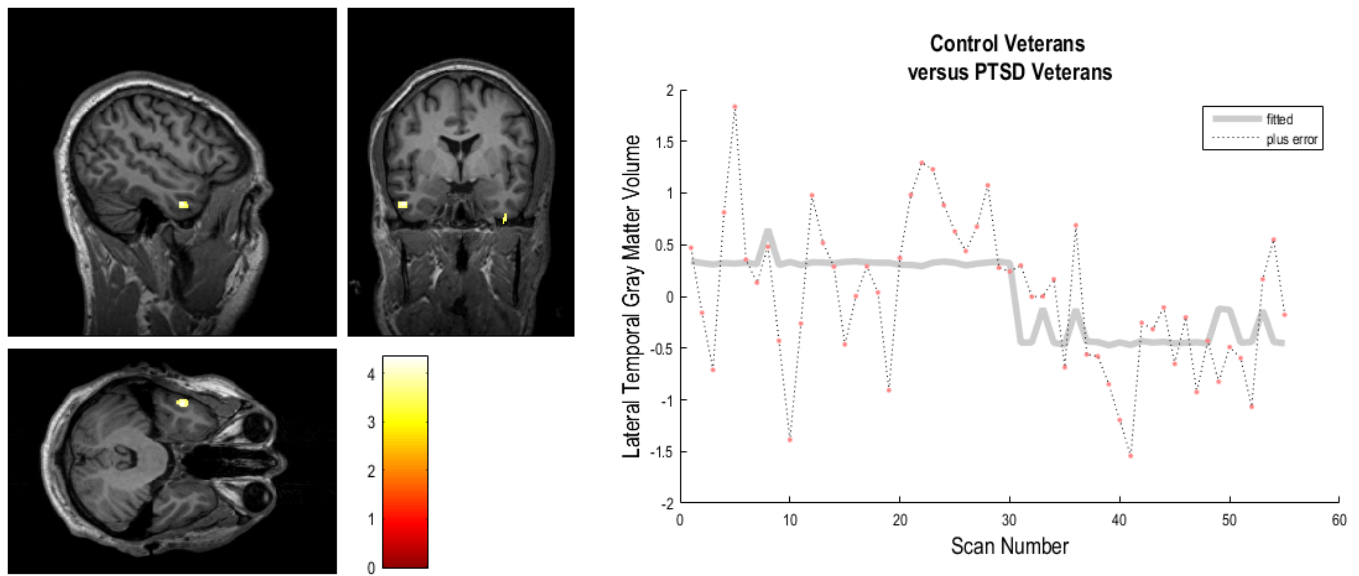


Figure 1. Study 1A: Non-PTSD veterans versus PTSD veterans. Left, the gray matter volume of a region in the left lateral temporal area (MNI coordinates: -43.5, -4.5, -28.5, 260 mm³, $p(\text{uncorrected}) < 0.001$) was significantly greater for non-PTSD veterans than for PTSD veterans, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). Right, gray matter volume of the left lateral temporal cluster is plotted on the y-axis against the scans of each individual. The first 30 scans represent non-PTSD veterans while the latter 25 represent PTSD veterans.

In the opposite direction, we found that PTSD veterans had significantly more gray matter volume in the midbrain area than non-PTSD veterans (MNI coordinates: 8, -24, -18, 71 mm³, $t(54) = 3.50$, $Z = 3.29$, $p(\text{uncorrected}) < 0.001$) (see Figure 2).

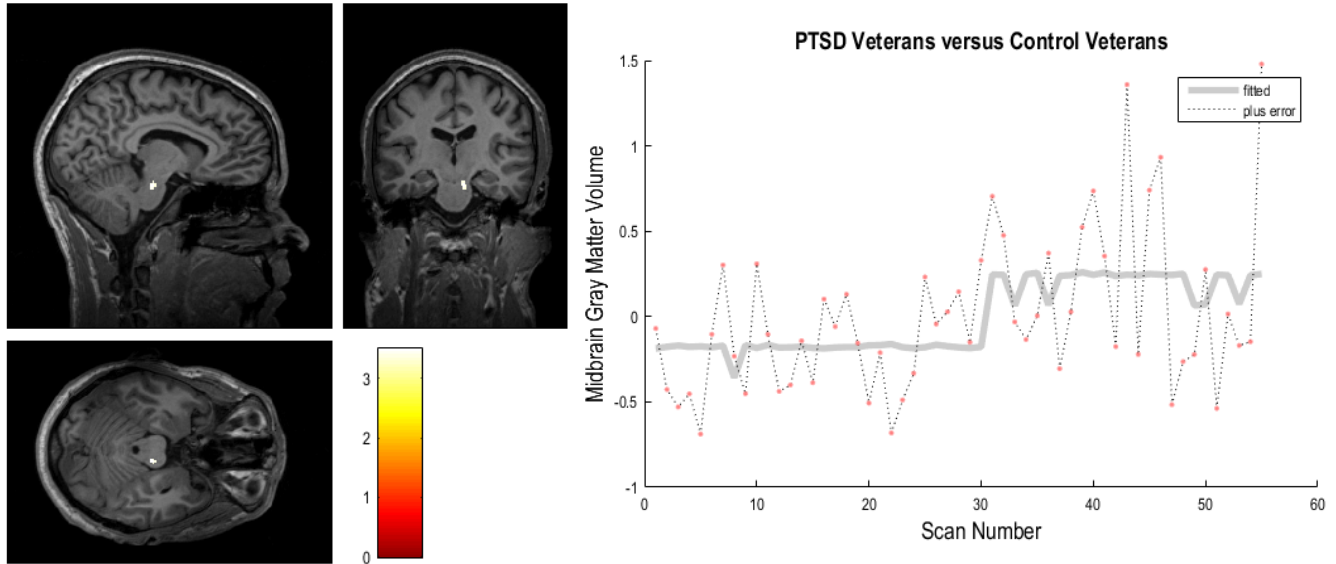


Figure 2. Study 1A: PTSD veterans versus non-PTSD veterans. Left, the gray matter volume of a region in the midbrain area (MNI coordinates: 8, -24, -18, 71 mm³, $p(\text{uncorrected}) < 0.001$) was significantly greater for PTSD veterans than for non-PTSD veterans, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). Right, gray matter volume of the midbrain cluster is plotted on the y-axis against the scans of each individual. The first 30 scans represent non-PTSD veterans while the latter 25 represent PTSD veterans.

Study 1B concentrated on healthy non-veteran controls versus the total veteran group (both PTSD and non-PTSD). Here, we found a significant difference in the gray matter volume of a cluster in the left frontal gyrus area (MNI coordinates: -44, 12, 11, 57 mm³, $t(78) = 3.86$, $Z = 3.67$, $p(\text{uncorrected}) < 0.001$), such that healthy controls had more gray matter volume in that region in comparison to all veterans in general (see Figure 3).

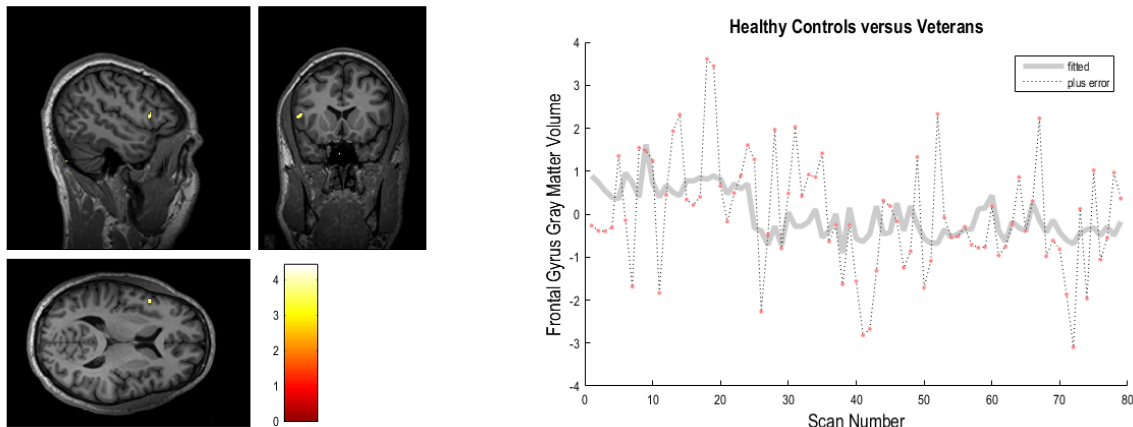


Figure 3. Study 1B: Healthy controls versus all veterans. Left, the gray matter volume of a region in the left frontal gyrus area (MNI coordinates: -44, 12, 11, 57 mm³, $p(\text{uncorrected}) < 0.001$) was significantly greater for healthy controls than for veterans, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). Right, gray matter volume of the left frontal gyrus cluster is plotted on the y-axis against the scans of each individual. The first 24 scans represent healthy controls, the middle 30 scans represent non-PTSD veterans, and the latter 25 represent PTSD veterans.

The final part of our first study, study 1C, focused on healthy controls versus PTSD veterans. We discovered a significant difference in the gray matter volume of a cluster in the left frontal gyrus area (MNI coordinates: -44, 12, 11, 30 mm³, $t(48) = 3.66$, $Z = 3.41$, $p(\text{uncorrected}) < 0.001$), such that healthy controls had more gray matter volume in that region in comparison to PTSD veterans. This result was consistent with our findings for study 1B. In addition, we also determined that healthy controls had a significantly greater amount of gray matter volume in clusters in the right medial frontal cortex area (MNI coordinates: 26, 20, 17, 91 mm³, $t(48) = 3.97$, $Z = 3.66$, $p(\text{uncorrected}) < 0.001$) and in the left orbitofrontal cortex area (MNI coordinates: -29, 47, -3, 95 mm³, $t(48) = 4.21$, $Z = 3.84$, $p(\text{uncorrected}) < 0.001$) than PTSD veterans (See Appendix C for corresponding figures). In the opposite direction, we found that PTSD veterans had more gray matter volume in the left intraparietal sulcus (MNI coordinates: -21, -54, 41, 61 mm³, $t(48) = 3.55$, $Z = 3.32$, $p(\text{uncorrected}) < 0.001$) than healthy controls (See Appendix D for corresponding figures).

In study 2, we investigated the gray matter structural correlates for symptom severity as well as each of the symptom clusters in the 5-factor model of PTSD. This analysis was focused only on the veteran population (both PTSD and non-PTSD). The PTSD patient assessment was compiled as a CAPS score and also broken down into the five separate factors of the model. These scores for both the total CAPS as well as the five symptom clusters were used in a VBM analysis. The first part of study 2, study 2A, involved using only the CAPS score—representing symptom severity—as a variable. We found that the gray matter volume of clusters in the midbrain (MNI coordinates: 8, -24, -17, 284 mm³, $t(54) = 3.95$, $Z = 3.67$, $p(\text{uncorrected}) < 0.001$) and the left posterior temporal (MNI coordinates: -48, -53, 0, 24 mm³, $t(54) = 3.65$, $Z = 3.43$, $p(\text{uncorrected}) < 0.001$) areas were significantly correlated with CAPS scores (see Figure 4).

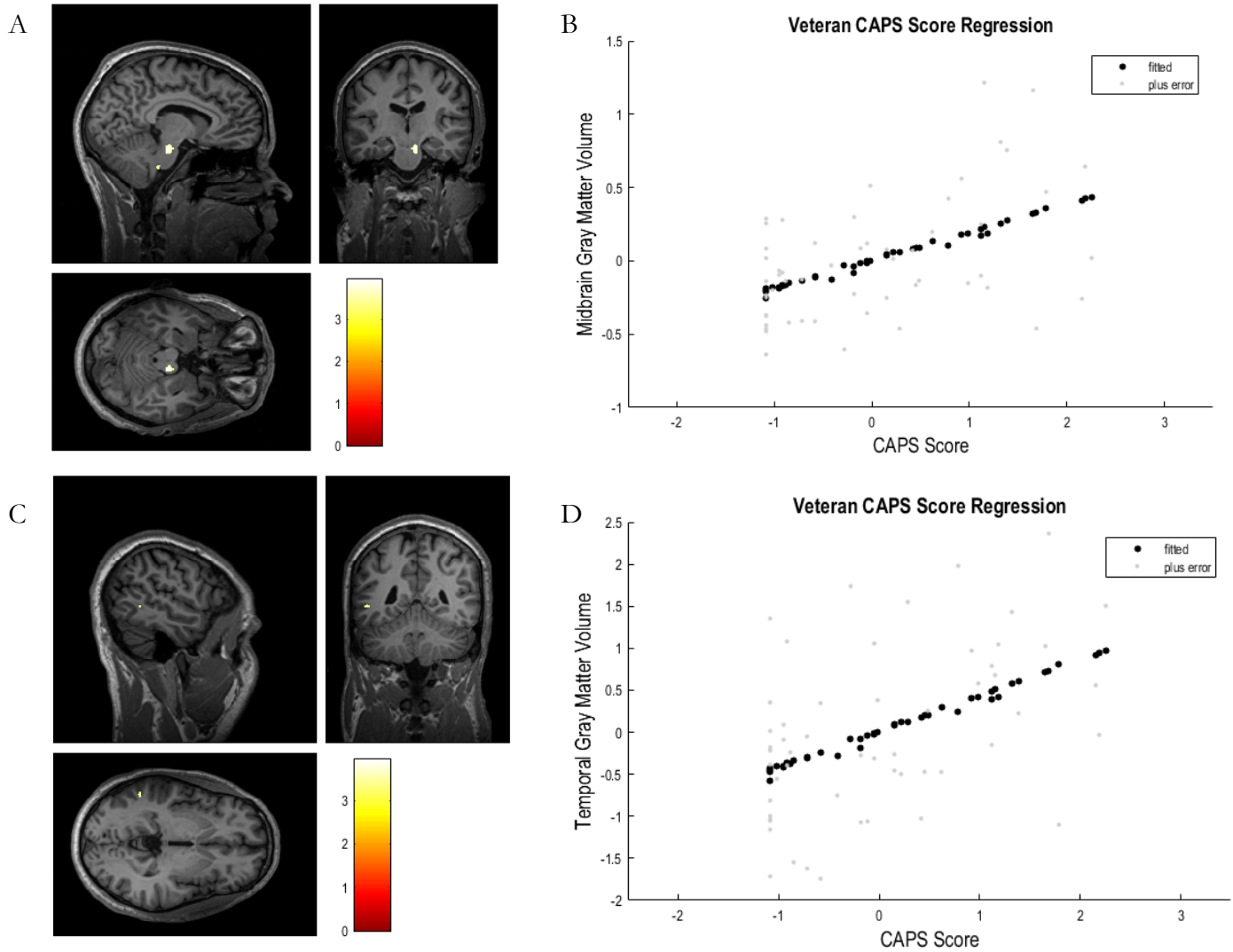


Figure 4. Study 2A: Veteran CAPS Score Regression. A) The gray matter volume of a region in the midbrain (MNI coordinates: 8, -24, -17, 284 mm³, $t(54) = 3.95$, $Z = 3.67$, $p(\text{uncorrected}) < 0.001$) was significantly correlated with CAPS scores, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). B) The gray matter volume of the midbrain cluster is plotted on the y-axis against the corresponding CAPS scores along with the fitted values. C) The gray matter volume of a region in the left posterior temporal (MNI coordinates: -48, -53, 0, 24 mm³, $t(54) = 3.65$, $Z = 3.43$, $p(\text{uncorrected}) < 0.001$) was significantly correlated with CAPS scores, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). D) The gray matter volume of the left posterior temporal cluster is plotted on the y-axis against the corresponding CAPS scores, along with the fitted values.

For study 2B, we analyzed the five symptom clusters within the 5-factor model of PTSD for the veteran population (both PTSD and non-PTSD). We found significant correlations for two factors: reexperiencing and anxious arousal. No other symptom clusters were significantly correlated with any gray matter volume in the brain. VBM analysis revealed that the gray matter volume of a cluster

in the superior parietal area was significantly correlated with the symptom factor of reexperiencing (MNI coordinates: 9, -51, 68, 17 mm³, $t(54) = 3.54$, $Z = 3.31$, $p(\text{uncorrected}) < 0.001$) (see Figure 5).

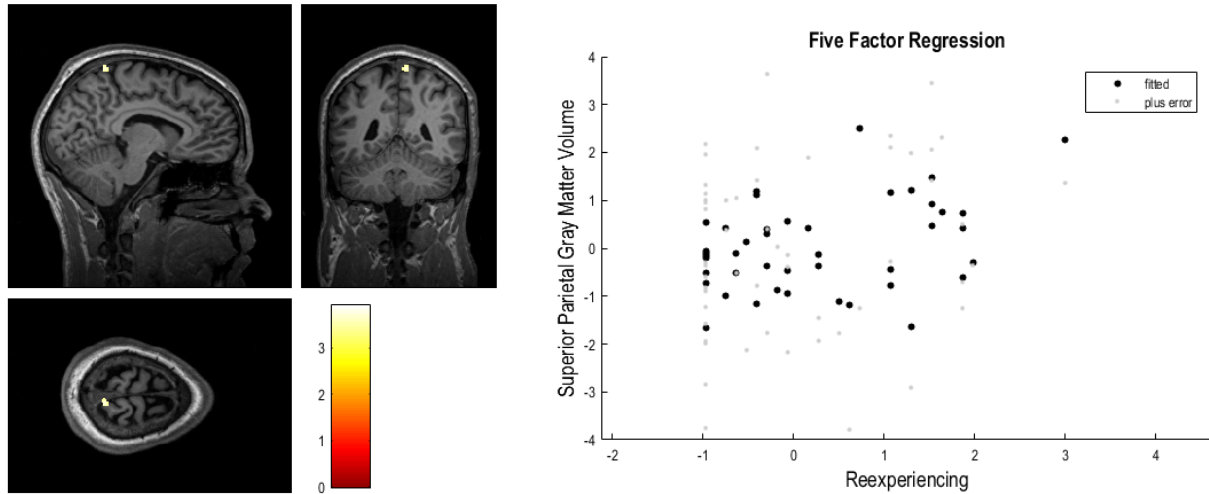


Figure 5. Study 2B: 5-Factor Regression: Reexperiencing. Left, the gray matter volume of a region in the superior parietal area (MNI coordinates: 9, -51, 68, 17 mm³, $t(54) = 3.54$, $Z = 3.31$, $p(\text{uncorrected}) < 0.001$) was significantly correlated with reexperiencing, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). Right, gray matter volume of the superior parietal cluster is plotted on the y-axis against the corresponding reexperiencing symptom scores, along with the fitted values.

Further analysis determined that the gray matter volume of clusters around the dorsolateral prefrontal cortex (MNI coordinates: 35, 45, 14, 14 mm³, $t(54) = 3.62$, $Z = 3.37$, $p(\text{uncorrected}) < 0.001$) and the supplementary motor area (MNI coordinates: 24, -12, 65, 10 mm³, $t(54) = 3.53$, $Z = 3.31$, $p(\text{uncorrected}) < 0.001$) were significantly correlated with the symptom factor of anxious arousal (see Figure 6).

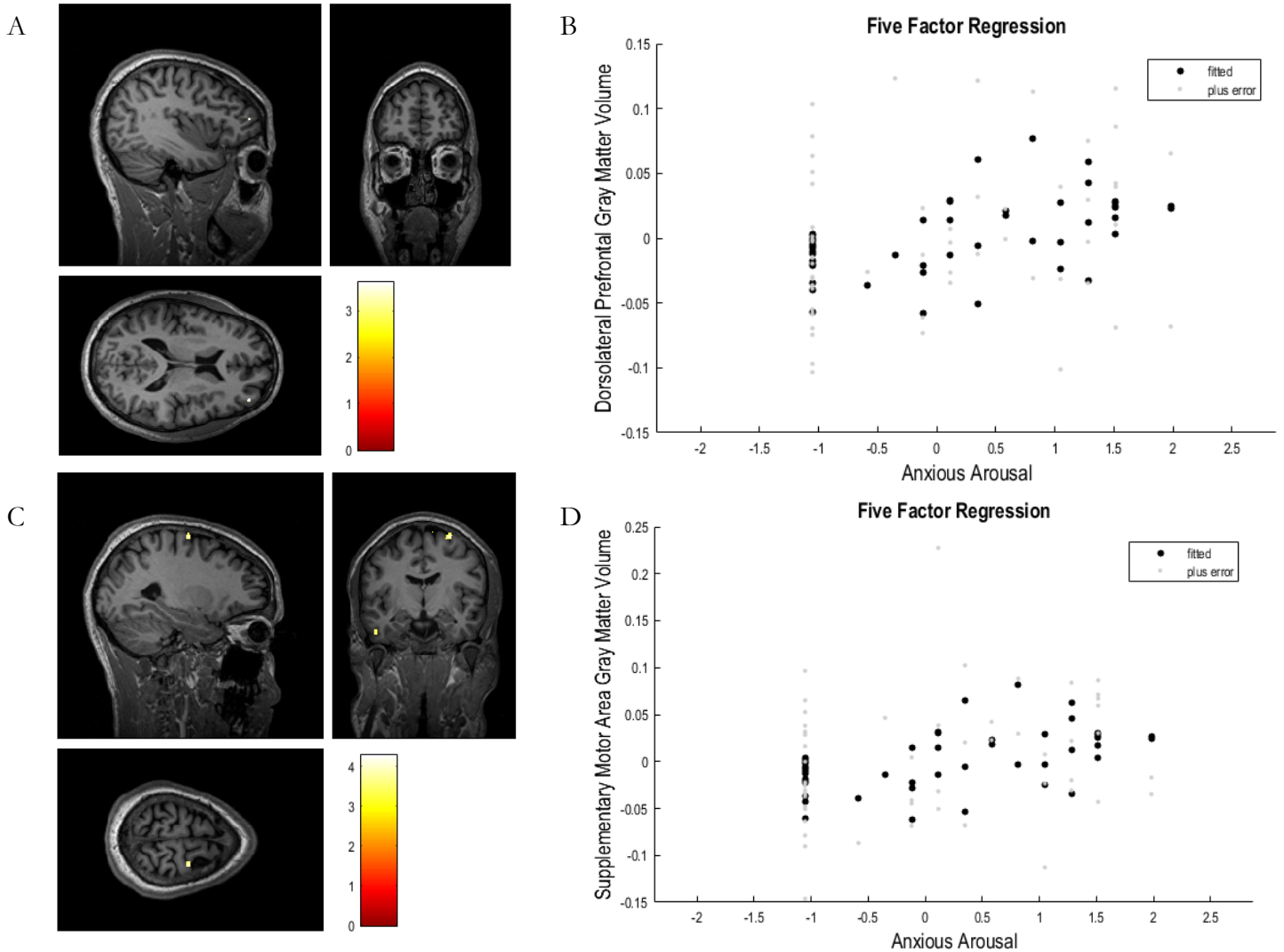


Figure 6. Study 2B: 5-Factor Regression: Anxious Arousal. A) The gray matter volume of a region around the dorsolateral prefrontal cortex (MNI coordinates: 35, 45, 14, 14 mm³, $t(54) = 3.62$, $Z = 3.37$, $p(\text{uncorrected}) < 0.001$) was significantly correlated with anxious arousal, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). B) Gray matter volume of the dorsolateral prefrontal cluster is plotted on the y-axis against the corresponding anxious arousal symptom scores, along with the fitted values. C) The gray matter volume of a region around the supplementary motor area (MNI coordinates: 24, -12, 65, 10 mm³, $t(54) = 3.53$, $Z = 3.31$, $p(\text{uncorrected}) < 0.001$) was significantly correlated with anxious arousal, as revealed by a voxel-based morphometry analysis (age, gender, and global volume controlled for). D) Gray matter volume of the supplementary motor area cluster is plotted on the y-axis against the corresponding anxious arousal symptom scores, along with the fitted values.

Summing up, our results show that there are structural brain differences based on group between PTSD veterans and non-PTSD veterans, healthy controls and all veterans, and healthy controls and PTSD veterans. Furthermore, our findings reveal a correlation between brain structure and symptom severity (in the form of CAPS scores) as well as neural correlates for two of the symptom clusters in the 5-factor model (reexperiencing and anxious arousal).

Discussion

The 5-factor model has developed into one of the best processes for assessing PTSD. Despite previous research into the structural differences in PTSD, no studies have investigated how each of the five factors—re-experiencing, avoidance, emotional numbing, dysphoric arousal, and anxious arousal—tie into specific neural alterations. Although structural neuroanatomical features of the human brain have been associated with PTSD and symptom severity, here we show for the first time that symptom clusters of the 5-factor PTSD model are correlated with the gray matter of neural structures. Reexperiencing appears to be correlated with the superior parietal area while anxious arousal is correlated with both dorsolateral prefrontal cortex and the supplementary motor area.

The superior parietal area has been implicated in top-down (voluntary) processes supporting memory retrieval search, monitoring, and verification (Cabeza, 2008). Our findings in this area corresponding to the reexperiencing symptom cluster could relate directly to the superior parietal area's role in memory. The dorsolateral prefrontal cortex has been shown to be functionally hypoactive in individuals with depression while the supplementary motor area has been linked to activations in fear conditioning studies (Koenigs, 2009; Etkin, 2011). This link to fear conditioning could reflect a variety of different processes and may not necessarily be directly related to the storage or retrieval of fear memory. But, our structural findings associated with anxiety arousal could still represent extensions of these previous results dealing with depression and fear.

The group level analyses also paint an interesting picture regarding PTSD. Our results indicated a structural difference between PTSD veterans and non-PTSD veterans, which suggests that, though trauma may still cause structural brain changes, PTSD symptoms themselves have a role in these differences as well. Our analysis of healthy controls versus all veterans also illustrated a

difference in structural volume in the left frontal gyrus, suggesting that trauma itself may cause certain structural changes. Our final group level analysis of healthy controls versus PTSD veterans revealed the largest number of significant structural differences, reinforcing the idea that both trauma and PTSD may engender their own structural neural changes.

The current study helps us tremendously in escaping the rigid “PTSD vs. non-PTSD” scheme in favor of a continuous inspection of symptoms. Different symptoms may require completely different treatments and currently we have quite an arbitrary definition of what constitutes PTSD. By uncovering certain biological markers that support the 5-factor model through this study, we will be able to determine a more concrete definition of PTSD. At the research level, our results will suggest that these factor delineations are “real”, at least for reexperiencing and anxious arousal; at the diagnostic level, our results may help provide objective tools in the future for determining PTSD by linking implicated structural volumes to certain symptom clusters; at the treatment level, our findings can help provide us with the first steps towards developing individualized treatments.

We hope that our findings will trigger a renewed impetus for investigating structural differences in the areas that are implicated in the 5-factor model. More specifically, we want to continue investigating these structures’ genetic determinants and environmental modulators, as well as determine whether these areas reflect an intrinsic vulnerability versus consequence of PTSD.

Though the applications and treatment implications stemming from this current study point in promising directions, any realistic clinical implications are tremendously far from actually being realized. A structural imaging approach to PTSD, coupled with other work delving into the functional aspects of the disorder, will hopefully grant us a more comprehensive understanding of the behavioral and neural mechanisms underlying the development and presence of PTSD. The

goal for this amalgamation of structural and functional analysis is to inform and refine behavioral and pharmacotherapeutic interventions designed to not only improve the quality of life for PTSD patients but to ultimately prevent the disorder in the first place (Levy I., personal communication). The primary advantages of the structural imaging approach lie in its potential to provide greater specificity regarding associations between structural volume, individual factors, and PTSD symptom severity in such a way as to bolster current models of PTSD. Enhanced models would in turn improve prevention and treatment approaches for this debilitating disorder. This current study also strongly portends structural imaging as an avenue for PTSD diagnostics. Pinpointing brain structure differences, especially broken down by specific factors from the 5-factor model may result in personalized MRI analyses relying on specific factor scores. Our research may also contribute to the discovery of a biological marker that can be used to assess a predisposition for the disorder. As a diagnostic tool, structural imaging may even become incorporated into everyday use as a tool to screen individuals for PTSD proclivity before sending soldiers into combat. Finally, brain structure analyses and structural volumetric measurements may potentially be more robust, cleaner determinants of PTSD symptom severity than current subjective behavioral assessments.

Despite the potential benefits derived from focusing on volumes of brain regions implicated in PTSD and ambiguity aversion, our structural research is hindered by certain major limitations. Since the hippocampus, the amygdala, and the anterior cingulate cortex are regions crucial for emotion and stress processing and have been implicated in previous structural studies, we expected to find similar patterns here. However, we failed to see any direct associations with these structures in our results. Moreover, ideally, we would have based all of our conclusions off of the corrected cluster-level p-values in our VBM analysis; however, there were no significant regions for the corrected significance levels so we were forced to rely on uncorrected p-values in assessing the significance levels of our results. This represent a red-flag that must be addressed in future research.

Accordingly, our current results may not be entirely robust. This failure to obtain significant corrected p-values for neural structures may have arisen from the fact that PTSD itself is quite inconsistent. The symptom landscape and individual factors are heavily influenced by the severity and length of time individuals have had the disease as well as the severity and length of time each specific symptom has been present. Thus, it is possible that the symptom scores can be quite volatile depending on the individuals themselves. If the symptomatology of our participants was abnormal, this could explain both our failure to obtain significant corrected cluster-level p-values as well as to replicate previous structural PTSD results.

Another area of obfuscation surrounding this structural study is distinguishing between the effects of trauma exposure versus structural predispositions to developing PTSD. How do we know whether the biological changes following trauma exposure are associated with PTSD and not simply with the trauma exposure itself? Furthermore, could a pre-existing brain abnormality predispose an individual to PTSD or to exposure to trauma, thereby helping us identify at-risk individuals? (Hull, 2002). The three possible interpretations of these structural deficits include: (1) a precursor risk factor for the exposure to a traumatic event that could then lead to PTSD; (2) a precursor vulnerability factor for the development of PTSD once a traumatic event is experienced; (3) the product of suffering from PTSD. In order to determine whether these deficits are indeed a product of PTSD, longitudinal studies with structural measures obtained pre-trauma are needed to ultimately disentangle predispositions from environmental factors (Kuhn, 2012). Thus, we cannot even begin to predict the causal direction of our current findings. However, if future studies can solve these mysteries, we may be able to engineer treatments to reverse structural regional brain alterations due to PTSD while also pre-screening individuals at-risk for PTSD by focusing on the areas that might predispose someone to developing PTSD.

A final limitation of our study lies in the nature of structural imaging itself. The raw data for neural structure volumetric differences is not well understood in terms of its importance at the neural level. Remarkably, we potentially know less about interpreting the results from structural imaging than those from functional MRI. We have yet to totally understand whether more or less volume (gray matter or subcortical volume) in certain brain regions and in certain situations leads to better or worse decision-making, memory, or emotion processing.

The data from this research has the potential to reveal new pathways for studying PTSD. In the future, we hope to expand on this research by using region-of-interest analysis to hone in on the hippocampus, amygdala, and ACC. In addition, a seven-factor model for PTSD has just recently emerged (Wang, 2015). It would be fascinating to compare this newest model to the five-factor model in terms of structural correlates. Long term, we hope to pursue a study recruiting combat soldiers at risk for trauma before they actually head out to combat. By taking structural scans and behavioral measurements of these pre-combat individuals before and after trauma, we will be able to analyze individuals who have experienced different types of traumas and trace any structural and/or behavioral changes that may have occurred as a direct result of these traumas, especially in their link to the five symptom clusters of the 5-factor model. This would provide a large step forward in illuminating the causal relationship dictating the interaction between structural volume, trauma, and PTSD symptom clusters.

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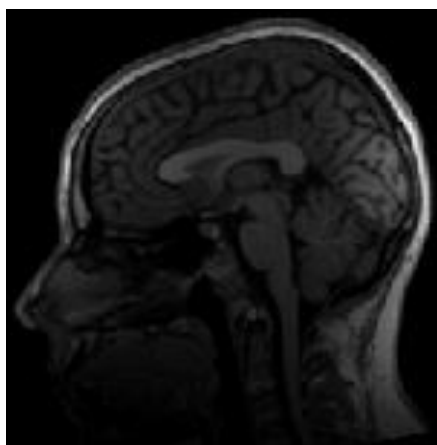
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Appendix A – Clinician-Administered PTSD Scale

Patient's name: _____						
Instruction to patient: Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem in the last month.						
No.	Response:	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1.	Repeated, disturbing memories, thoughts, or images of a stressful experience from the past?					
2.	Repeated, disturbing dreams of a stressful experience from the past?					
3.	Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)?					
4.	Feeling very upset when something reminded you of a stressful experience from the past?					
5.	Having physical reactions (eg, heart pounding, trouble breathing, or sweating) when something reminded you of a stressful experience from the past?					
6.	Avoid thinking about or talking about a stressful experience from the past or avoid having feelings related to it?					
7.	Avoid activities or situations because they remind you of a stressful experience from the past?					
8.	Trouble remembering important parts of a stressful experience from the past?					
9.	Loss of interest in things that you used to enjoy?					
10.	Feeling distant or cut off from other people?					
11.	Feeling emotionally numb or being unable to have loving feelings for those close to you?					
12.	Feeling as if your future will somehow be cut short?					
13.	Trouble falling or staying asleep?					
14.	Feeling irritable or having angry outbursts?					
15.	Having difficulty concentrating?					
16.	Being "super alert" or watchful on guard?					
17.	Feeling jumpy or easily startled?					
Total score:						

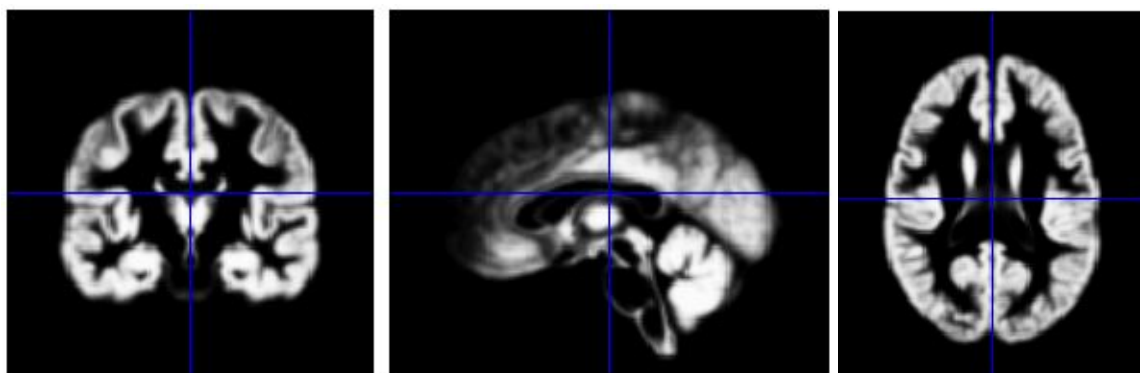
Appendix B – Preprocessing Steps



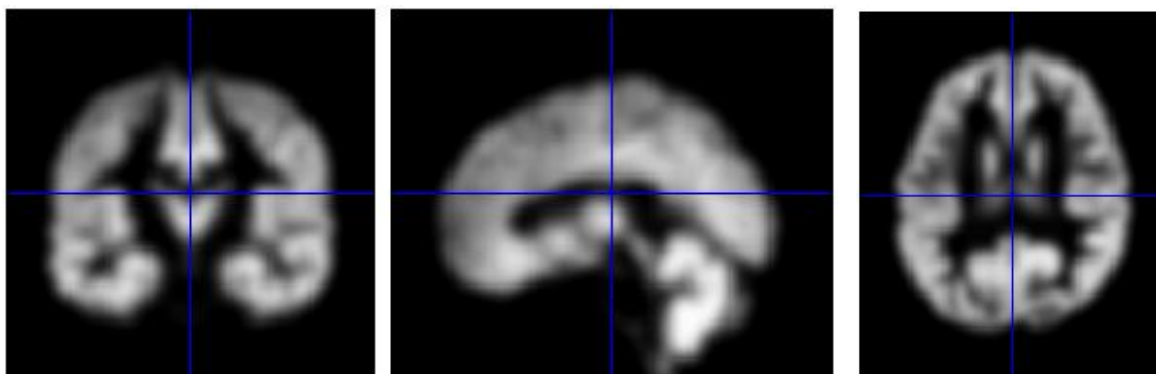
1: Realignment



2: Gray Matter Segmentation

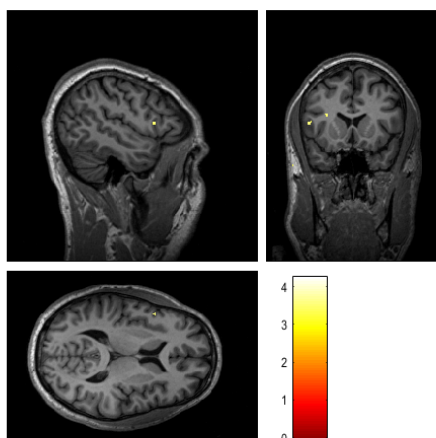


3: DARTEL Template

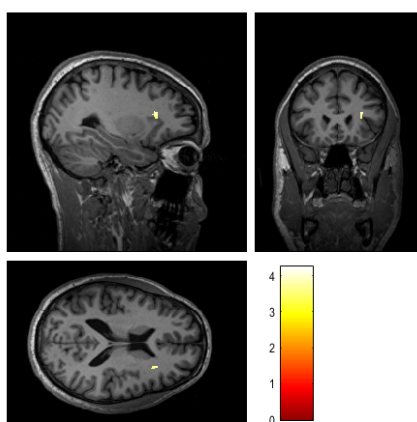
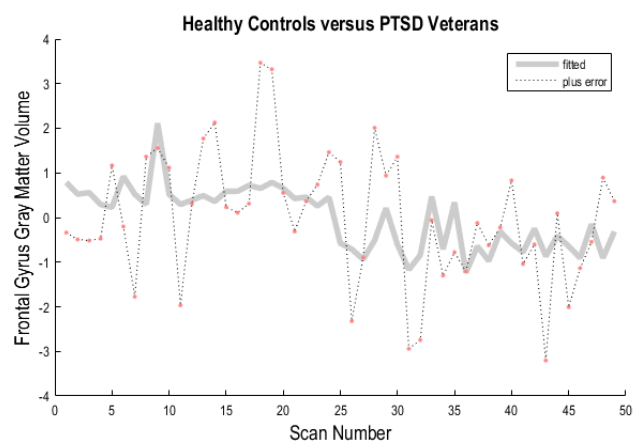


4: MNI Normalization

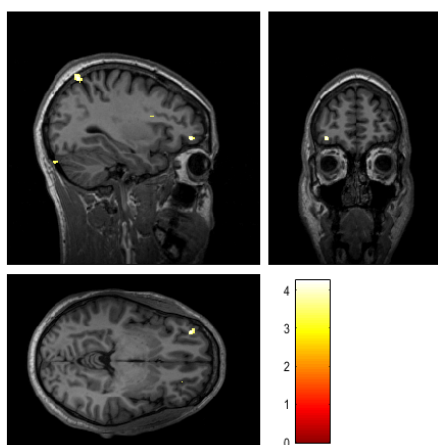
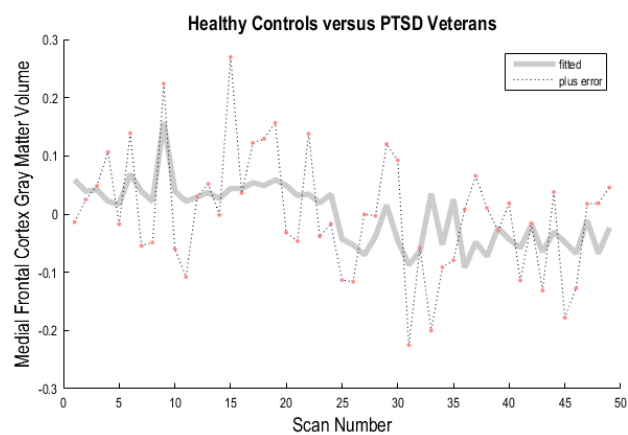
Appendix C – Study 1C Results: Healthy Controls versus PTSD Veterans



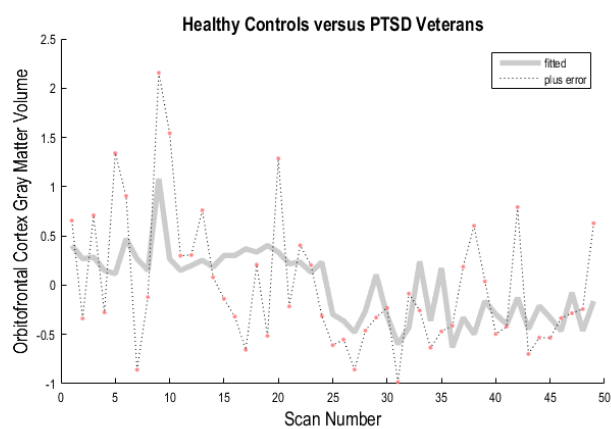
Left Frontal Gyrus



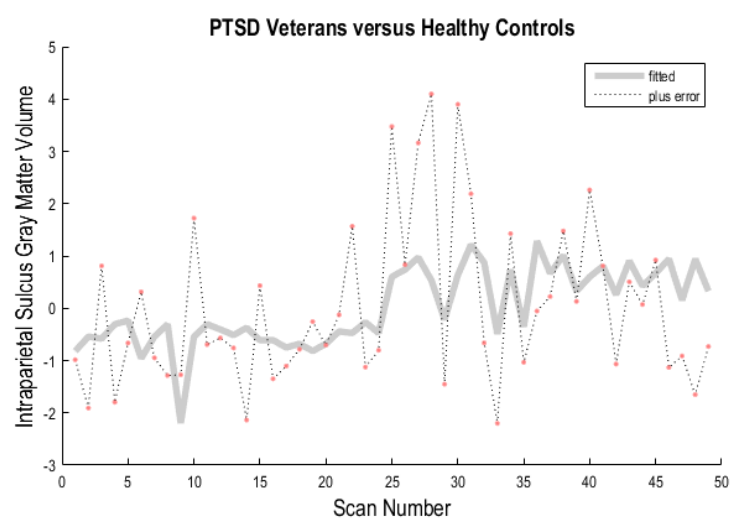
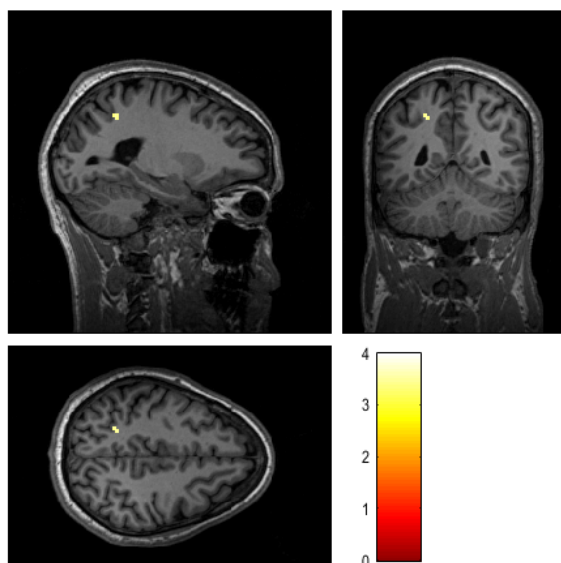
Medial Frontal Cortex



Orbitofrontal Cortex



Appendix D – Study 1C Results: PTSD Veteran versus Healthy Controls



Left Intraparietal Sulcus