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Post-Traumatic Stress Disorder symptom sub-cluster severity predicts gray matter volume changes better than overall symptom severity

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INTRODUCTION

Post-Traumatic Stress Disorder (PTSD) is largely understood as a dysregulation of the neural circuitry underlying fear extinction learning – specifically, mediated by amygdala hyperresponsivity and inadequate top-down control of the amygdala by medial prefrontal cortex (including the ventromedial prefrontal, subcallosal, and orbitofrontal cortices) and hippocampus. Magnetic Resonance Imaging (MRI) studies report decreased volumes of hippocampus, rostral anterior cingulate cortex, subcallosal cortex, and insula in PTSD compared to controls, suggesting decreased top-down control of amygdala responsivity in PTSD (Rauch et al. 2006; Kasai et al. 2008).

However, PTSD is not a unitary, homogeneous disorder; some symptoms do not have direct fear-related correlates. Such symptoms include anhedonia, emotional numbing, and substance abuse. In light of these fear-unrelated symptoms, Stein and Paulus (2009) have proposed that PTSD is an imbalance disorder characterized by a failure to successfully adapt systems mediating approach (i.e. reward-related circuitry) and avoidance (i.e. fear-related circuitry). Key PTSD symptoms can be readily associated with approach and avoidance: Dysphoria symptoms suggest downregulated approach, while Hyperarousal and Avoidance symptoms suggest upregulated avoidance behavior.

Recent meta-analysis of studies examining PTSD factors derived from literature (Yufik & Simms, 2010) determined that the latent structure of PTSD was best characterized by the four factors of Re-experiencing, Avoidance, Dysphoria, and Hyperarousal. However, it remains unclear whether symptom sub-clusters are differentially associated with the volumetric changes observed in PTSD.

This study examines the relationship between symptom sub-cluster severity and changes in gray matter volume (GMV) in survivors of interpersonal violence who were diagnosed with PTSD, while accounting for age-associated GMV changes.

METHODS

11 females (mean age 38.4 years) who had been diagnosed with PTSD resulting from interpersonal violence participated in an MRI study. Following neuropsychiatric testing, individuals with current substance dependence, lifetime or current psychosis, bipolar disorder, current suicidality, and current psychoactive medications were excluded from the study. A T1-weighted 3D MPRAGE volume was acquired in the MRI scanner at Georgetown University (Siemens 3T Tim Trio, 176 sagittal slices, TR/TE=1900/2.52ms, effective resolution 1mm^3). Participants' PTSD severity was assessed using the PTSD Checklist (PCL; Weathers 1993).

Volumetric data analysis was conducted in the Voxel-Based Morphometry (VBM) stream within SPM5 (Ashburner 2000). Given previous findings of abnormal regional gray matter volumes in PTSD as discussed above, we isolated our analyses to the gray matter volume.

Severity of overall PTSD and symptom "sub-clusters" of Avoidance, Dysphoria, Hyperarousal, and Re-experiencing factors were calculated according to Krause et al. (2007). Overall PTSD was correlated with GMV, regressing out effects of age, and was thresholded at $p < 0.01$ uncorrected, cluster size $k > 20$. For each sub-cluster, a multivariate linear regression was performed, modeling subcluster severity as a covariate of interest while controlling for effects of age on GMV. Results were thresholded at p=0.0025, uncorrected, with cluster size $k > 20$. Coordinates are reported in Talairach space.

VBM RESULTS: SUBCLUSTER SEVERITY

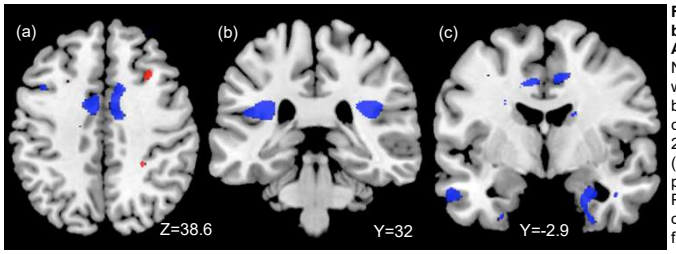

Figure 1. Association between GMV and Avoidance Sub-cluster. Negative correlations were observed in bilateral (a) anterior/mid-cingulate gyrus (BA32/24) and (b) insula (BA13), and in (c) right parahippocampal gyrus. Positive correlation was observed in right mid-frontal gyrus (BA8). Negative correlations were also observed in left inferior temporal gyrus (BA20), left middle occipital gyrus (BA18), left precentral gyrus (BA6), right inferior orbitofrontal gyrus (BA11), right mid-frontal gyrus (BA9), and right superior frontal gyrus (BA6). Positive correlation was also observed in left claustrum.

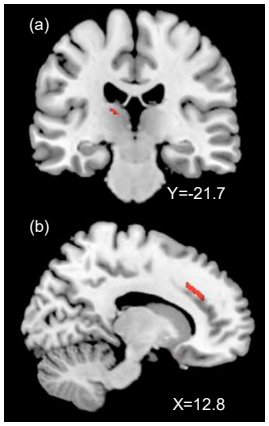

Figure 2. Association between GMV and Hyperarousal Sub-cluster. Positive correlations were observed in (a) left thalamus, (b) right cingulate gyrus (BA32) and right inferior parietal cortex (BA40, not shown).

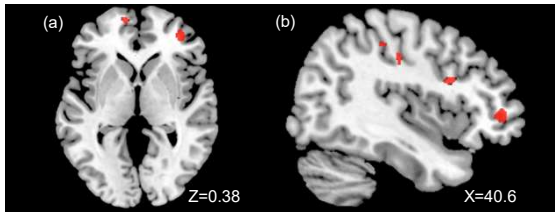

Figure 3. Association between GMV and Dysphoria Sub-cluster. Dysphoria severity was positively correlated with GMV in (a) right mid-frontal gyrus (BA8,10), left superior frontal gyrus (BA10), and (b) right post-central gyrus (BA3).

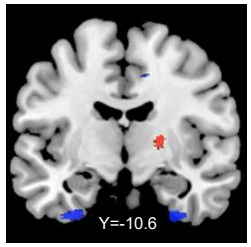

Figure 4. Association between GMV and Re-experiencing Sub-cluster. Negative correlation was observed in bilateral inferior temporal gyrus (BA20), and positive correlation was observed in right globus pallidus.

Negative correlations were also observed in left inferior frontal gyrus (BA44), left insula (BA13, BA47), left inferior parietal lobule (BA40), left precuneus (BA5), and left lingual/occipital cortex (BA17,18). Positive correlation was also observed in left putamen.

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VBM RESULTS: TOTAL PTSD SEVERITY

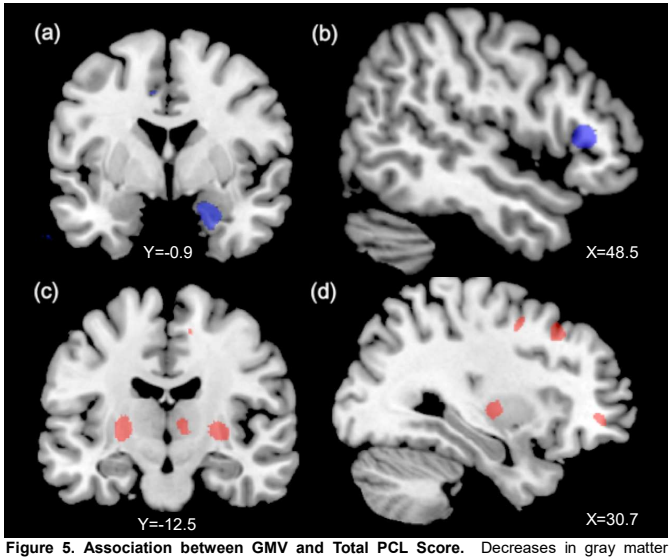

Figure 5. Association between GMV and Total PCL Score. Decreases in gray matter associated with increasing PTSD severity (i.e. PCL score) were observed in (a) right parahippocampal gyrus and (b) right inferior frontal gyrus (BA45). Positive correlations between GM volume and PTSD severity were observed in regions of (c) bilateral globus pallidus, right thalamus, and (d) right mid-frontal gyrus (BA8). Results are displayed at p<0.01, uncorrected, whole-brain level.

CONCLUSIONS

Sub-cluster analyses revealed changes in GMV that were not associated with total PTSD severity in our analyses but have been associated with PTSD in prior studies. Avoidance (avoidant thinking, behavior) was negatively correlated with bilateral insula and anterior/mid-cingulate cortices (Rauch et al. 2006). Dysphoria (emotional numbing, difficulty concentrating) was positively correlated with GMV in the mid-frontal gyrus, as previously reported in depression (van Tol et al. 2010; Kroes et al. 2011a). Re-experiencing (flashbacks, nightmares, reliving) was associated with bilateral GMV decrease in the inferior temporal gyrus, extending prior findings that decreased volume in this region is associated with PTSD flashbacks (Kroes et al. 2011b). In line with Lanius et al. 2006, severity of the Hyperarousal sub-cluster (hypervigilant, "jumpy") was associated with GMV increases in the left thalamus, right anterior/mid-cingulate, as well as right inferior parietal cortex.

Our results also suggest that GMV changes associated with total PTSD severity can be explained in terms of difffering contributions of clusters of symptoms. Decreased GMV in right parahippocampal and inferior frontal gyri is explained by severity of Avoidance symptoms; increased GMV in globus pallidus by Re-experiencing symptom severity; increased thalamic GMV by Hyperarousal symptom severity, and increased right midddle frontal GMV by Dysphoria symptom severity.

Overall, our findings indicate that examining symptom sub-cluster severities may provide greater insight into the brain structure abnormalities seen in PTSD, with implications for the understanding and treatment of this heterogeneous disorder.