



# Connectome-wide investigation of altered resting-state functional connectivity in war veterans with and without posttraumatic stress disorder



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## ABSTRACT

Altered resting-state functional connectivity in posttraumatic stress disorder (PTSD) suggests neuropathology of the disorder. While seed-based fMRI connectivity analysis is often used for the studies, such analysis requires defining a seed location *a priori*, which restricts search scope and could bias findings toward presupposed areas. Recently, a comprehensive exploratory voxel-wise connectivity analysis, the connectome-wide association approach, has been introduced using multivariate distance matrix regression (MDMR) for resting-state functional connectivity analysis. The current study performed a connectome-wide investigation of resting-state functional connectivity for war veterans with and without PTSD compared to non-trauma-exposed healthy controls using MDMR.

Thirty-five male combat veterans with PTSD (unmedicated), 18 male combat veterans without PTSD (veterans control, VC), and 28 age-matched non-trauma-exposed healthy males (NC) participated in a resting-state fMRI scan. MDMR analysis was used to identify between-groups differences in regions with altered connectivity. The identified regions were used as a seed for post-hoc functional connectivity analysis.

The analysis revealed that PTSD patients had hypoconnectivity between the left lateral prefrontal regions and the salience network regions as well as hypoconnectivity between the parahippocampal gyrus and the visual cortex areas. Connectivity between the ventromedial prefrontal cortex and the middle frontal gyrus and between the parahippocampal gyrus and the anterior insula were negatively correlated with PTSD symptom severity. VC subjects also had altered functional connectivity compared to NC, including increased connectivity between the posterior insula and several brain regions and decreased connectivity between the precuneus region and several other brain areas.

The decreased connectivity between the lateral prefrontal regions and the salience network regions in PTSD was consistent with previous reports that indicated lowered emotion-regulation function in these regions. The decreased connectivity between the parahippocampal gyrus and visual cortex supported the dual representation theory of PTSD, which suggests dissociation between sensory and contextual memory representations in PTSD. The theory also supposes that the precuneus is a region that triggers retrieval of sensory memory of traumatic events. The decreased connectivity at the precuneus for VC might be associated with suppressing such a process.

## 1. Introduction

Posttraumatic stress disorder (PTSD) is one of the most prevalent mental disorders for war veterans. A screening for mental health problems by the US military suggested 9.8% of veterans returning from Iraq, 4.7% from Afghanistan, and 2.1% from other locations were at risk of PTSD (Hoge et al., 2006). Several studies have suggested a

biological basis for PTSD (Pitman et al., 2012 for review), including neuroimaging studies (e.g., Hayes et al., 2012; Lanius et al., 2006; Liberzon and Sripada, 2008; Patel et al., 2012). Nonetheless, ongoing research is needed to better understand the complex neurobiological abnormalities that underlie this costly and chronic condition.

One of the types of neuroimaging studies that is providing abundant insights into the neuropathology of intrinsic brain activity in PTSD is

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resting-state functional magnetic resonance imaging (rsfMRI), which measures blood oxygenation level dependent (BOLD) signal while a subject does not perform any explicit task. This includes studies using voxel-wise resting-state signal measurement such as amplitude of low-frequency fluctuation (ALFF) (Zou et al., 2008) and regional homogeneity (ReHo) (Zang et al., 2004). Meta-analyses of these studies combined with positron emission tomography (PET) studies (Koch et al., 2016; Wang et al., 2016) showed that PTSD patients had increased resting-state signal fluctuation or activity in the amygdala and the parahippocampal gyrus and decreased fluctuation or activity in the superior frontal gyrus and the middle frontal gyrus, although there is significant variability across studies. Decomposition of spatial coactivation patterns, such as independent component analysis (ICA), was also used in an rsfMRI study (Calhoun and Adali, 2012). Although ICA is typically employed to extract the spatial pattern of a functional network, it can also be used to evaluate connectivity with a dual regression technique (Filippini et al., 2009), in which correlations between the global network (independent component) time-course and voxel-wise time-courses are examined. Tursich et al. (2015) indicated that the connectivity of the salience network (SN) with the posterior insula and the superior temporal gyrus were negatively correlated with hyperarousal symptoms in PTSD. Graph analysis for resting-state connectivity (Fornito et al., 2013) was also employed in an rsfMRI study of PTSD (Lei et al., 2015), indicating that the resting-state functional network for PTSD shifted toward small-worldization with increased centrality in the default-mode network (DMN) and the SN.

Another commonly employed measure of rsfMRI is functional connectivity (Friston, 1994), which evaluates the correlation of signal time-courses between a seed region and other brain regions. Seed-based connectivity analyses also showed aberrant resting-state connectivity for PTSD. Brown et al. (2014) indicated increased connectivity between the basolateral amygdala and the anterior cingulate cortex (ACC), dorsal ACC, and dorsomedial prefrontal cortex as well as decreased connectivity between the amygdala and the left inferior frontal gyrus for PTSD patients compared to trauma-exposed controls. Zhang et al. (2016) found decreased connectivity between the ventral anterior insula and the ACC, and between the right posterior insula and the left inferior parietal lobe and the postcentral gyrus. Kennis et al. (2015) showed decreased connectivity between the caudal ACC and the precentral gyrus and between the perigenual ACC and the superior medial frontal gyrus and middle temporal gyrus.

These findings suggest several converging regions of pathological resting-state activity or connectivity for PTSD such as hyperactivity and increased connectivity in the SN regions, including the amygdala, anterior insula, and ACC, and hypoactivity and decreased connectivity in the prefrontal emotion-regulation areas including lateral prefrontal regions and dorsal and ventral medial prefrontal regions. Deficits in emotion regulation function due to hyperactive and hyperconnected SN and its hypoconnectivity with lateral prefrontal regions are thought to underlie the hyperarousal symptoms of PTSD (Fonzo et al., 2010; Lanius et al., 2006; Zhu et al., 2015).

A limitation of previous functional connectivity studies, however, is that seed-based resting-state connectivity analysis requires the a priori definition of a seed location. This restricts the scope of investigation to relations with the presupposed seed area and could bias findings toward the seed area. In particular, a priori predictions about the functioning of regions implicated in emotion regulation may have resulted in the overrepresentation of these regions in our current understanding of resting state functional connectivity in PTSD. Indeed, abnormal brain functioning in PTSD is not limited to the emotion regulation network. Task-based fMRI studies have suggested abnormal functioning in regions implicated in attention and working memory (Aupperle et al., 2012) as well as memory representation (Brewin, 2011; Whalley et al., 2013), such as the medial temporal and posterior brain regions including hippocampal, parietal, and occipital areas. Those low-level sensorimotor regions are rarely identified as seeds for functional connectivity

analyses in studies of PTSD. While voxel-wise whole-brain investigations of resting-state activity with ALFF, ReHo, and PET (Bonne et al., 2003; Kohn et al., 2014; Wang et al., 2016) often suggested altered resting-state activity in the sensorimotor, visual cortex, and hippocampal/parahippocampal areas, these measures did not elucidate functional connectivity of the regions. Connectivity analysis using ICA also does not capture region-by-region functional connectivity. Instead, it analyzes connectivity between a global brain network and a voxel-wise signal.

To complement these analyses, and to resolve the limitation of seed-based connectivity analysis, yet another rsfMRI analysis has been proposed: a connectome-wide approach that investigates comprehensive voxel-wise connectivity alterations (Shehzad et al., 2014). This approach utilizes a multivariate distance matrix regression (MDMR) analysis (Anderson, 2001) and can examine voxel-wise connectivity alterations in the whole brain without a priori seed definition. Satterthwaite et al. (2015) applied this analysis to major depressive disorder (MDD), PTSD, and female healthy control subjects and found that decreased connectivity between the amygdala and the dorsolateral prefrontal cortex, ACC, and anterior insula correlated with depression symptom severity. They also showed that elevated connectivity between the amygdala and the ventromedial prefrontal cortex correlated with anxiety symptom severity.

The aim of this study was to examine altered resting-state connectivity of male war veterans with and without PTSD and male age-matched non-trauma-exposed healthy controls using a connectome-wide approach. We expected connectome-wide investigation of altered resting-state functional connectivity to reveal a comprehensive view of the neuropathology of intrinsic brain functional connectivity among people with PTSD without bias introduced via hypothesis testing.

In addition to examining veterans with combat-related PTSD, we also examined altered resting-state connectivity among combat veterans without PTSD. While a population with trauma experience without PTSD has often been considered a control group for understanding atypical functioning among people with PTSD, several studies have demonstrated atypical brain activation in this group compared to non-trauma-exposed people. For example, war-deployed soldiers who did not develop PTSD showed lowered midbrain activation in a working memory task and decreased connectivity between the midbrain region and the prefrontal cortex compared to non-deployed soldiers (van Wingen et al., 2012). Meta-analysis of region-wise resting-state brain activation (Patel et al., 2012) indicated higher prefrontal activity among trauma-exposed people without PTSD compared to non-trauma-exposed controls. A resting-state functional connectivity analysis with an ACC seed (Kennis et al., 2015) also indicated that war veterans without PTSD had a different pattern of resting-state connectivity compared to civilian controls. The differences include decreased connectivity between the caudal ACC and the precentral gyrus and between the perigenual ACC and the superior medial frontal and the middle temporal gyrus, and increased connectivity between the rostral ACC and precentral and middle frontal regions. These data suggest that war veterans without PTSD could have altered intrinsic brain activation compared to both people with PTSD and non-trauma-exposed controls. Importantly, altered brain functioning in PTSD and trauma-exposed controls may not be incremental. Trauma-exposed controls without PTSD could have a specific brain alteration that does not exist in PTSD, which may function as an adaptive change to trauma exposure or as a protective factor that reduces the likelihood of developing PTSD subsequent to trauma exposure. The current study, therefore, employed three groups of male subjects: war veterans with PTSD (unmedicated), war veterans without PTSD, and age-matched non-trauma-exposed healthy controls. The study examined comprehensive connectome-wide differences in resting-state functional connectivity between these groups.

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