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## Neural Dysregulation in Posttraumatic Stress Disorder: Evidence for Disrupted Equilibrium between Salience and Default Mode Brain Networks

Rebecca K. Sripada, M.S.<sup>a,b</sup>, Anthony P. King, Ph.D.<sup>b</sup>, Robert C. Welsh, Ph.D.<sup>b,c</sup>, Sarah N. Garfinkel, Ph.D.<sup>e</sup>, Xin Wang, M.D.<sup>b</sup>, Chandra S. Sripada, M.D.<sup>b</sup>, and Israel Liberzon, M.D.<sup>a,b,d</sup>

<sup>a</sup>Psychology, University of Michigan, Ann Arbor, MI

<sup>b</sup>Psychiatry, University of Michigan, Ann Arbor, MI

<sup>c</sup>Radiology, University of Michigan, Ann Arbor, MI

<sup>d</sup>Ann Arbor VA Medical Center, Ann Arbor, MI

<sup>e</sup>Brighton and Sussex Medical School, Brighton, United Kingdom

### Abstract

**Objective**—Convergent neuroimaging and neuropsychological research demonstrates disrupted attention and heightened threat sensitivity in PTSD. This might be linked to aberrations in large-scale networks subserving detection of salient stimuli, i.e. the salience network (SN), and stimulus-independent, internally-focused thought, i.e. the default mode network (DMN).

**Methods**—Resting state brain activity was measured in returning veterans who served in Iraq or Afghanistan with (n=15) and without PTSD (n=15) and in healthy community controls (n=15). Correlation coefficients were calculated between the time course of seed regions in key SN and DMN regions (posterior cingulate, ventromedial prefrontal cortex, and bilateral anterior insula) and all other voxels of the brain.

**Results**—Compared to control groups, PTSD participants showed reduced functional connectivity within DMN (between DMN seeds and other DMN regions), including rostral ACC/vmPFC ( $Z=3.31$ ;  $p=.005$ , corrected) and hippocampus ( $Z=2.58$ ;  $p=.005$ ), and increased connectivity within SN (between insula seeds and other SN regions), including amygdala ( $Z=3.03$ ;  $p=.01$ , corrected). PTSD participants also demonstrated increased cross-network connectivity. DMN seeds exhibited elevated connectivity with SN regions, including insula ( $Z=3.06$ ;  $p=.03$ , corrected), putamen, and supplementary motor area ( $Z=4.14$ ;  $Z=4.08$ ;  $p<.001$ ), and SN seeds exhibited elevated connectivity with DMN regions, including hippocampus ( $Z=3.10$ ;  $p=.048$ , corrected).

**Conclusions**—During resting state scanning, PTSD participants showed reduced coupling within DMN, greater coupling within SN, and increased coupling between DMN and SN. Our findings suggest a relative dominance of threat-sensitive circuitry in PTSD, even in task-free

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Corresponding Author: Rebecca K. Sripada, 4250 Plymouth Road, 2702 Rachel Upjohn Building, Ann Arbor MI 48109, telephone: 734-232-0190, fax: 734-936-7868, rekaufma@umich.edu.

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conditions. Disequilibrium between large-scale networks subserving salience detection versus internally focused thought may be associated with PTSD pathophysiology.

## Keywords

PTSD; default mode network; salience network; functional connectivity; resting-state; fMRI

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## Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder characterized by re-experiencing, avoidance and hyperarousal symptoms (1). These symptoms have been linked to deficits in attentional control (2–4), threat sensitivity (5–7), episodic memory (8–10), and fear extinction (11, 12), functions subserved by cortico-subcortical circuits involving amygdala, insula, ventromedial prefrontal cortex (vmPFC) and hippocampus (13, 14). While the activation patterns of these regions have been examined extensively in the past, identifying dysregulated patterns of connectivity between these regions could shed important and unique light on the brain-basis of PTSD (15, 16), and on previously unexplained mechanisms of PTSD symptom development.

Regions implicated in PTSD (e.g., insula, amygdala, vmPFC, hippocampus) are key nodes in several major intrinsic connectivity networks (ICNs). ICNs are large-scale networks identified by connectivity methods that are associated with characteristic functions (17, 18), are stable across tasks (19, 20) and over time (21, 22), correspond to anatomical white matter tracts (23), and demonstrate direct behavioral correlates (24–26). Insula and amygdala, which have been found to be hyperactive in PTSD (15, 16), are involved in the salience network (SN), an ICN responsible for detecting and orienting to salient stimuli (27–30). A second important ICN, the default mode network (DMN) is associated with stimulus-independent, internally focused thought and autobiographical memory (31–33). VMPFC and hippocampus, regions reported to be hypoactive in PTSD during specific tasks (16), along with the posterior cingulate cortex (PCC), are core components of this network (17, 28). A third ICN, the central executive network (CEN), encompasses dlPFC and lateral parietal regions. This network is associated with goal-directed behavior and high level cognitive function, including planning, decision-making, and working memory (27, 30). It has been suggested that SN “arbitrates” between DMN and CEN (34). SN regions assess the significance or salience of stimuli the organism encounters, and help to maintain an adaptive balance between internal mentation and externally-oriented focus and task execution.

Recently, functional connectivity analyses have begun to be used to probe network-level function in PTSD. During task-based studies, PTSD patients show exaggerated connectivity within DMN regions and reduced connectivity within SN and CEN regions (35). These relationships might potentially be better assessed, however, through connectivity analyses at rest, without the confounds of tasks that may be biased to elicit amygdala activity or provoke PTSD symptoms. Resting-state connectivity offers a powerful way to assess intrinsic connections between brain networks (17, 36, 37), which in turn have been linked to important functions such as processing speed (26) and cognitive flexibility (38) in health and in disease. During rest, disrupted connectivity within DMN and SN has been reported in PTSD (39–44) and acute stress disorder (45, 46). However, no research to date has used the ICN framework to investigate the relationship between DMN, SN and CEN at rest in PTSD. Identifying abnormal interrelationships between these networks could illuminate the disruptions in attention regulation and balance of internal/external sensitivity characteristically found in PTSD, including abnormalities underlying symptoms of hyperarousal.

Given findings that PTSD patients show alterations in functions linked to DMN and SN, we hypothesized disruptions in the balance between these networks in task-free resting-state, when DMN is typically active and SN and CEN are quiescent. Given aberrations in episodic memory in PTSD, we hypothesized reduced connectivity within DMN. Given heightened threat sensitivity, impaired attentional control, and hyperarousal in PTSD, functions associated with SN connectivity (27, 47, 48), we hypothesized increased connectivity within SN, and reduced segregation (that is, increased cross-network connectivity) between DMN regions and SN regions.

## Methods and Materials

### Participants

We recruited study participants from among veterans returning from deployments to Afghanistan (Operation Enduring Freedom; OEF) and Iraq (Operation Iraqi Freedom; OIF) with a current PTSD diagnosis and seeking treatment for PTSD at the VA Ann Arbor Healthcare System (n=15), along with veterans without PTSD (combat-exposed controls; n=15), and 15 healthy controls from the community. All procedures took place between August 2008 and July 2010. Healthy controls and combat controls (veterans of OEF and OIF without PTSD) were recruited from the community via advertisement. All participants received comprehensive psychiatric assessment with the Mini-International Neuropsychiatric Interview (M.I.N.I.; 49), which contains a PTSD module, and self-report instruments. Combat veterans also received the Clinician Administered PTSD Scale (CAPS; 50). Clinical interviews were performed by experienced Masters or PhD-level clinicians with extensive training in the CAPS, at a subspecialty clinic specializing in PTSD. PTSD participants were provided with the opportunity to participate in research at the time of their initial VA visit, and all interested eligible participants were included in the study. All participants in the PTSD group met DSM-IV criteria for current (past month) PTSD. All combat exposure (including index trauma for PTSD participants) took place within the past five years. Exclusion criteria were: 1) psychosis, 2) history of traumatic brain injury, 3) alcohol or substance abuse or dependence in the past 3 months, 4) any psychoactive medication other than sleep aids, 5) left-handedness, 6) presence of ferrous-containing metals within the body, and 7) claustrophobia. Control groups included only participants without DSM-IV psychiatric diagnoses, and the healthy community control group included only participants who had not experienced a traumatic event. Demographic and clinical characteristics of the participants are shown in Table 1. All subjects were right-handed males between 21 and 37 years old. Seven participants in the PTSD group also met diagnostic criteria for comorbid depression and one had comorbid panic disorder, however in no case could comorbid diagnosis be considered primary, i.e. preceding PTSD. Two PTSD participants were using low dose trazodone as a sleep aid; no other psychiatric medications were permitted. After a complete description of the study was provided to the participants, written informed consent was obtained. The study was approved by the Institutional Review Boards of the University of Michigan Medical School and the Ann Arbor Veterans Affairs Healthcare System.

### Resting State Paradigm

Participants underwent structural (sMRI) and functional (fMRI) scanning that included resting state procedures and emotion regulation and conditioning tasks. Reports on emotion regulation and conditioning tasks are forthcoming; a report of amygdala-seed resting state functional connectivity has been previously published (43). Resting-state scans always occurred prior to tasks. A black fixation cross on a white background was displayed at the center of the screen for 10 minutes. Participants were instructed to relax and keep their eyes

open and fixed on the cross. To control for physiological variation, multiple regression was used to remove the effects of cardiac and respiratory signals (51).

## Data Analysis

Scans were collected on a 3.0 Tesla General Electric Signa® Excite™ scanner (Milwaukee, WI). Further details are provided in Supplemental Digital Content 1. Default mode ROIs (PCC and vmPFC) were 10 mm radius spheres centered at (0,−56,20) for PCC and (−2,48,−4) for vmPFC. These seed regions were adopted from previous studies of the DMN in PTSD (40, 45), schizophrenia (52), and healthy controls (17). Salience network ROIs (bilateral anterior insula) were partitioned from a whole insula mask using linear interpolation based on the location of the middle insular gyrus, following Aupperle and colleagues (53). We extracted spatially averaged time series from each ROI for each participant. Average BOLD time series from subject-specific structural MRI-derived white matter and cerebrospinal fluid masks were added to the model as nuisance covariates to control for non-specific global sources of noise associated with BOLD fMRI scanning. We did not perform global-signal regression, as it had been suggested that this may produce spurious anti-correlation with orthogonal networks that increase in proportion to the size of the those networks (54). Resting state functional connectivity measures low-frequency spontaneous BOLD oscillations (.01 – .10 Hz band) (17), thus, the time-course for each voxel was band-passed filtered in this range. Pearson product-moment correlation coefficients were calculated between average time courses in the seed regions of interest (ROIs) and all other voxels of the brain resulting in a 3-dimensional correlation coefficient image (r-image). Both positive correlations and anti-correlations were computed. These r-images were then transformed to z-scores using a Fisher r-to-z transformation (55).

Z-score images from the individual functional connectivity analyses were entered into second-level random-effects analyses (one-sample and two-sample t-tests) implemented in SPM5. Second-level maps were thresholded at  $p < .001$ , uncorrected, extent threshold  $k = 10$ . In addition, region of interest analysis with small volume correction (SVC) was conducted. A priori ROIs including the amygdala ( $k = 93$ ), hippocampus ( $k = 252$ ), anterior cingulate cortex (ACC;  $k = 838$ ), and insula ( $k = 499$ ) were used as masks, as these regions are of interest in PTSD (15, 16). Images were thresholded using a voxelwise threshold of  $p < .005$  uncorrected with a minimum cluster size of 3 connected voxels (for amygdala clusters), 4 connected voxels (for hippocampus clusters), 6 connected voxels (for insula clusters), and 12 connected voxels (for ACC clusters). These combinations of activation threshold and cluster size were determined using AlphaSim (56) to correspond to a false positive rate of  $p < .05$ , corrected for multiple comparisons within ROIs. Using the thresholds and cluster sizes defined above, the corrected voxel-wise probabilities are as follows: amygdala  $p < .0016$ , hippocampus  $p < .00098$ , insula  $p < .00045$ , and ACC  $p < .00072$ . Only the activations within the ROIs that survived the volume and voxel correction criteria were extracted and used for further analysis. Connectivity foci were labeled by comparison with the neuroanatomical atlas by Talairach and Tournoux (57). Reported voxel coordinates correspond to standardized Montreal Neurologic Institute (MNI) space. To assess for correlations with symptom severity, CAPS scores were added as regressors in a separate whole brain analysis of connectivity between seed regions and ROIs, corrected for multiple comparisons across four seed regions. Finally, we conducted an exploratory conjunction analysis (58) to determine whether regions of group difference with one ICN seed-region showed overlap with the other ICN (e.g. regions of differential group connectivity with DMN seed regions falling within SN, and vice versa).

Motion parameters (maximum displacement, mean displacement, maximum angle, mean angle) were compared via Independent-Samples Kruskal-Wallis tests.

## Results

### Participants

While levels of combat exposure were not different in the returning veterans with and without PTSD, PTSD symptoms (CAPS scores) in the healthy combat-exposed control group were low, and significantly lower than the PTSD group. Groups did not differ by age or race, however there was a trend for marital status such that PTSD participants were more likely to be married than healthy community or combat controls ( $p=.08$ ; see Table 1).

### Motion

There were no movements greater than 3 millimeters and no motion differences between groups (in all cases  $p>.2$ ).

### FMRI findings

In the following paragraphs, we focus on comparisons between the PTSD group and Combat-exposed Controls and Healthy Community Controls combined (“Controls”). Of note, single group results and two-group comparisons between the PTSD group and individual control groups are presented in SDC1, Tables S1 through S5.

### PTSD versus Controls

**PCC**—In comparison to controls, PTSD participants showed greater functional connectivity between PCC seed and right putamen ([24,-9,3];  $k=30$ ;  $Z=4.13$ ;  $p<.001$ ) and right insula ([39,15,-3];  $k=6$ ;  $Z=3.06$ ;  $p=.03$ , SVC). Compared to PTSD participants, controls showed greater connectivity between PCC seed and left hippocampus at trend level ([-27,-15,-18];  $k=5$ ;  $Z=2.58$ ;  $p=.005$ ; see Figure 1 and Figure 2; Table 2).

**vmPFC**—Compared to controls, PTSD participants showed greater functional connectivity between the vmPFC seed and precentral sulcus/supplementary motor area ([15,-15,72];  $k=26$ ;  $Z=4.08$ ;  $p<.001$ ), right precentral gyrus ([54,-12,27];  $k=12$ ;  $Z=3.7$ ;  $p<.001$ ), and bilateral superior temporal sulcus ([-51,-66,12];  $k=12$ ;  $Z=3.51$ ; [48,-57,12];  $k=13$ ;  $Z=4.15$ ;  $p<.001$ ). Compared to PTSD participants, controls showed greater connectivity between vmPFC seed and rostral anterior cingulate cortex ([-12,27,27];  $k=20$ ;  $Z=3.31$ ;  $p=.005$ , SVC; see Figure 2; Table 2).

**Left anterior insula**—Compared to controls, PTSD participants showed greater functional connectivity between the left anterior insula seed and left peri-insula/superior temporal gyrus ([-48,-33,21];  $k=11$ ;  $Z=3.54$ ;  $p<.001$ ), right hippocampus ([36,-12,-15];  $k=12$ ;  $Z=3.10$ ;  $p=.048$ , SVC), and right amygdala ([24,6,-18];  $k=5$ ;  $Z=3.03$ ;  $p=.01$ , SVC; see Figure 2; Table 2). For left anterior insula, controls did not show significantly greater functional connectivity than PTSD participants in any regions.

**Right anterior insula**—There were no significant group differences in right anterior insula connectivity between the PTSD and combined control group. Please see SDC1 for comparisons to individual control groups.

### Correlations with Symptom Severity

**PCC**—Within the PTSD group, functional connectivity between PCC seed and precentral sulcus was positively correlated with symptom severity as measured by the CAPS ([-9,-6,72];  $k=7$ ;  $Z=3.79$ ;  $r=.88$ ,  $p<.001$ ; corrected for comparisons at multiple seed regions), as well as CAPS subscales (Intrusive subscale:  $r=.72$ ,  $p=.009$ , Avoidance subscale:  $r=.64$ ,  $p=.03$ , Hyperarousal subscale:  $r=.69$ ,  $p=.01$ ).

**vmPFC**—Within the PTSD group, functional connectivity between vmPFC seed and left hippocampus was negatively correlated with total CAPS score ( $[-33, -21, -12]$ ;  $k=12$ ;  $Z=3.9$ ;  $r=-.89$ ,  $p<.001$ ; corrected for multiple comparisons), as well as CAPS subscales (Intrusive subscale:  $r=-.71$ ,  $p=.004$ , Avoidance subscale:  $r=-.68$ ,  $p=.007$ , Hyperarousal subscale:  $r=-.75$ ,  $p=.002$ ).

**Left anterior insula**—There were no significant correlations between left anterior insula connectivity and total CAPS score in the PTSD group.

**Right anterior insula**—Within the PTSD group, functional connectivity between right anterior insula seed and right peri-insula/rolandic operculum was positively correlated with symptom severity as measured by the CAPS ( $[57, -6, 18]$ ;  $k=6$ ;  $Z=4.47$ ;  $r=.67$ ,  $p<.001$ ; corrected for multiple comparisons), as well as CAPS subscales (Intrusive subscale:  $r=.6$ ,  $p=.02$ , Avoidance subscale:  $r=.56$ ,  $p=.04$ ).

### Conjunction Analysis

A conjunction analysis was performed comparing the map of functional connectivity with a PCC seed, PTSD participants > controls, and control group connectivity with an anterior insula seed. Results showed overlap in right putamen ( $[27, -6, 3]$ ;  $k=30$ ) and right thalamus ( $[9, -21, 6]$ ;  $k=18$ ).

Functional connectivity with a vmPFC seed, PTSD participants > controls, was compared with a map of control group connectivity with an anterior insula seed. Results showed overlap in precentral sulcus ( $[18, -12, 72]$ ;  $k=8$ ), right superior temporal sulcus ( $[51, -54, 9]$ ;  $k=7$ ), and left superior temporal sulcus ( $[-51, -60, 9]$ ;  $k=8$ ).

### Discussion

In this study, we investigated patterns of resting-state default and salience network functional connectivity, comparing military combat veterans deployed to Iraq or Afghanistan (OEF/OIF) with PTSD versus OEF/OIF combat-exposed healthy veterans and healthy community controls. To our knowledge, this is the first study to systematically examine the relationship between the SN and DMN ICNs in PTSD during rest, and the first to examine resting-state DMN functional connectivity in combat veterans. Overall, we found reduced connectivity within DMN, increased connectivity within SN, and increased connectivity between DMN regions and SN regions in PTSD subjects. The results suggest a possible brain basis for exaggerated attention to external stimuli, potentially contributing to hypervigilance and hyperarousal symptoms of PTSD.

Our within group findings (presented in SDC1) are highly consistent with existing models of DMN and SN functional connectivity (17, 31, 32, 37). We found strong functional connectivity in healthy control groups (i.e., combat controls and community controls) between PCC and vmPFC seeds and other DMN regions, including angular gyrus, lateral temporal lobe, and hippocampus. The DMN is associated with stimulus-independent thought, including spontaneous cognition, autobiographical memory, and mind-wandering (59), thus this network is active during non-structured tasks. DMN seed regions also showed expected anti-correlation with regions of the SN (including insula, inferior frontal gyrus, and supplementary motor area) (27). Our analysis also revealed high functional connectivity between SN seeds (bilateral anterior insula) and other SN regions, including dorsal ACC/supplementary motor area, amygdala, and striatum, along with anti-correlation between SN seeds and DMN regions including PCC, vmPFC, and hippocampus. The SN is associated with attention to external stimuli, and though SN is co-active with DMN during certain tasks (60), it typically anti-correlates with DMN during rest (17, 61, 62). Our results thus confirm

existing models that suggest that rest and other non-structured activities require deactivation of attentional and executive processes reflected by anti-correlation between DMN and SN.

Compared to control groups, PTSD participants showed reduced functional connectivity between DMN seeds and other DMN regions, including rostral ACC/vmPFC and hippocampus, consistent with a previous study in PTSD (40), as well as another study in OCD (63). These regions are also hypoactive in PTSD during tasks (16) including script-driven imagery, trauma-relevant and trauma-irrelevant negative stimuli (15). Thus, our results suggest that regions underactive in PTSD in a variety of task-based contexts also fail to incorporate into resting-state networks, potentially indicating more general disruptions in self-referential thought in PTSD. Our findings add to a growing body of evidence suggesting that in PTSD there is weakened DMN functional integration during resting-state (40, 41, 46), and alterations in DMN function more generally (35, 39). Though the implications of this dysfunction remain to be further investigated, it may suggest that default mode functioning is hampered by hyperarousal and avoidance, or that abnormal interconnectedness between DMN and SN contributes to these symptoms. Indeed, within our PTSD sample, less DMN connectivity to hippocampus was associated with higher CAPS score (total score, as well as reexperiencing, avoidance and hyperarousal subscales). Thus, reduced cohesiveness of DMN may be associated with greater symptom severity in PTSD.

PTSD participants also demonstrated greater functional connectivity between SN seeds and other SN regions, including insula, peri-insula, and amygdala. The SN is associated with homeostatic regulation, interoceptive, autonomic, and reward processing (27, 28, 34, 64), functions known to be dysregulated in anxiety disorders (65, 66). Greater within-SN connectivity may reflect exaggerated sustained attention to extraneous stimuli. In activation studies, co-occurring increases in insula and amygdala activity are greater in PTSD than in control groups during trauma reminders (67) and fear acquisition (68), and a recent meta-analysis confirms patterns of disrupted DMN and SN in PTSD during structured tasks (69). Recently we have reported that individuals with PTSD show greater intrinsic connectivity between amygdala and insula at rest (43), potentially reflecting a tighter functional link between visceral perception and emotional response. Our findings complement those of Daniels and colleagues (35), who report ICN alterations in PTSD during a working memory task. However, while Daniels et al. reported decreased within-network SN connectivity and increased within-network DMN connectivity during task, we found increased within-network SN connectivity and decreased within-network DMN connectivity during rest. This discrepancy might reflect differences in the balance between ICNs during cognitively demanding tasks (where CEN and SN are predominant) versus rest (where DMN is predominant). Thus Daniels and colleagues' study and our own both suggest aberrant ICN activity in PTSD. In our analysis, greater functional connectivity between SN seed regions and peri-insula/operculum was associated with higher CAPS score, further supporting the hypothesis that pervasive SN activity during task-free states may be involved in PTSD psychopathology.

In addition to weakened within-network DMN connectivity and exaggerated within-network SN connectivity, PTSD participants also demonstrated increased cross-network connectivity between DMN regions and SN regions. In PTSD, as compared to controls, SN seed regions showed increased connectivity to left hippocampus, part of DMN. In turn, DMN seed regions showed increased connectivity to SN regions of insula, putamen, and supplementary motor area, as well as posterior superior temporal sulcus. The superior temporal sulcus, though not previously implicated in the SN, is an associative area that shows strong resting-state functional connectivity with SN regions including supplementary motor area, insula, and striatum (70), thus it may contribute to SN function. A conjunction analysis confirmed

that regions showing exaggerated connectivity with DMN in PTSD were constituents of the SN in control groups. Enhanced cross-network connectivity in PTSD between DMN and regions of SN has also been shown in prior studies. For example, elevated connectivity in PTSD has been observed between thalamus (a key SN node) and DMN (71). Additionally, enhanced connectivity between DMN and amygdala predicted the development of PTSD symptoms in acutely traumatized individuals (45), and enhanced connectivity between DMN and insula was associated with higher self-report anxiety (72).

The SN supports monitoring of salient cognitive, homeostatic, or emotional events, and is typically anti-correlated with DMN during rest (27, 73). Thus our results indicate a disruption of equilibrium between these networks, or diminished network segregation. In particular, the co-activation of SN with DMN might reflect sustained and likely inappropriate activation of SN during periods of rest, when this network is typically quiescent. This finding may reflect or help to explain sustained hypervigilance and hyperarousal in PTSD patients. Indeed, in our sample, greater functional connectivity between DMN seeds and supplementary motor area, an important node in the SN network, was correlated with enhanced hyperarousal symptoms (and total PTSD symptoms). Our results are thus consistent with previous findings of disrupted cortico-subcortical connectivity in PTSD (45, 71, 72), and extend these findings by revealing an underlying dysfunction in the balance between ICNs.

The functional impact of disrupted resting-state connectivity has been debated. Disrupted ICN segregation could be related to the development of other symptoms or physiological abnormalities in PTSD. For instance, greater intrinsic connectivity in the SN is associated with higher self-report anxiety (27) and greater HPA axis responsivity to aversive stimuli (47). Disruptions in the equilibrium between ICNs may affect regulatory efficiency, particularly alterations in SN, which plays a role in switching between other large-scale networks (34). Finally, weaker anti-correlation between DMN and its anti-correlated networks (both at task and at rest) is associated with diminished performance in a cognitive interference task (26) and a psychomotor vigilance task (48). Taken together, these findings suggest that disequilibrium between ICNs is a pervasive phenomenon that may affect PTSD patients across a variety of contexts.

This study has several limitations. First, our sample size was small, thus our results should be considered preliminary. Second, seed voxel-based resting state connectivity provides an important method to assess connectivity within specific networks, but it is essentially correlational and thus does not allow for inferences about causal relationships. Activation differences and connectivity differences cannot be disentangled using seed-based connectivity measures. Since we did not collect measures of mental activity during the resting state scan, we cannot discern whether differential engagement in various cognitive processes could be driving the observed group differences. Third, since only male veterans with combat exposure were included in this study, generalizations to women or to non-combat related PTSD should be made with caution. Fourth, our PTSD sample included participants with co-morbid major depression. Though depression commonly co-occurs with PTSD in veteran populations (up to 80% by some estimates: 74), inclusion of depressed participants may render some of the variance attributable to the presence of depression. However, our results were not affected by the removal of participants with current comorbid depression (see Supplemental Results in SDC1). Therefore, we retained depressed participants in our final analysis. In conclusion, this study found reduced coupling within DMN, increased coupling within SN, and increased coupling between DMN and SN in PTSD participants during resting-state. These findings may reflect a dominance of threat-sensitive circuitry in PTSD, even in task-free conditions. Our results suggest that



disequilibrium between large-scale networks subserving salience detection versus internally focused thought may be associated with PTSD pathophysiology.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

|              |   |
|--------------|---|
| <b>PTSD</b>  | posttraumatic stress disorder                 |
| <b>vmPFC</b> | ventromedial prefrontal cortex                |
| <b>ICN</b>   | intrinsic connectivity networks               |
| <b>DMN</b>   | default mode network                          |
| <b>PCC</b>   | posterior cingulate cortex                    |
| <b>CEN</b>   | central executive network                     |
| <b>SN</b>    | salience network                              |
| <b>OEF</b>   | Operation Enduring Freedom                    |
| <b>OIF</b>   | Operation Iraqi Freedom                       |
| <b>MINI</b>  | Mini-International Neuropsychiatric Interview |
| <b>CAPS</b>  | Clinician Administered PTSD Scale             |
| <b>sMRI</b>  | structural MRI                                |
| <b>fMRI</b>  | functional MRI                                |

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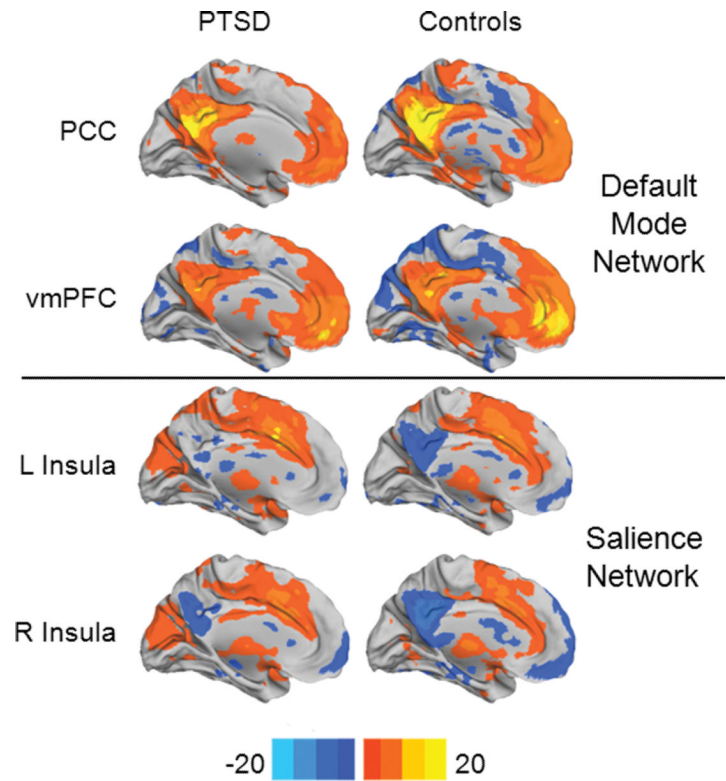
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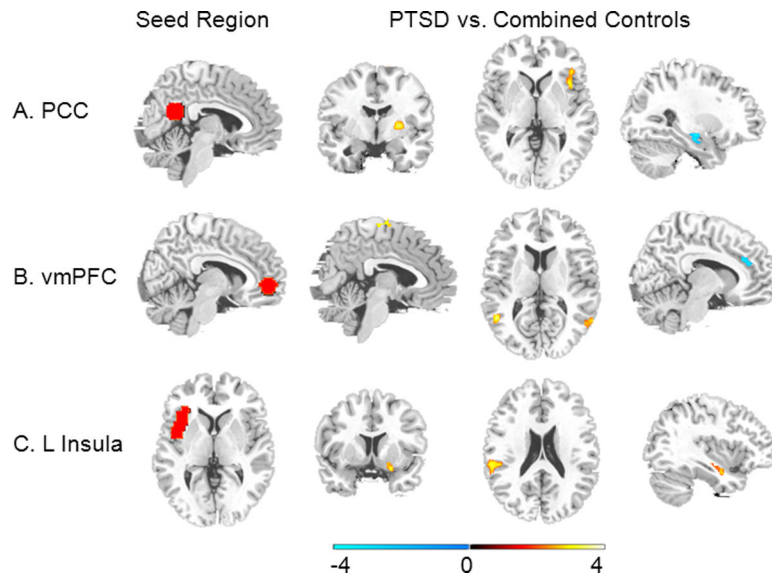
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**Figure 1. Functional connectivity analysis**

Statistical significance (color-coded  $t$  score) of resting-state functional connectivity patterns for Default Mode Network (PCC seed and vmPFC seed) and Salience Network (left anterior insula seed and right anterior insula seed) for 15 PTSD participants and 30 Controls (15 combat-exposed controls and 15 healthy community controls). PCC: posterior cingulate cortex; vmPFC: ventromedial prefrontal cortex.



**Figure 2. Group Comparison**

(A) Compared to controls, PTSD participants showed greater connectivity between posterior cingulate cortex (PCC; seed region shown in A) and right putamen (column 2;  $y = -4$ ) and right insula (column 3;  $z = 2$ ) and a trend for less connectivity between PCC seed and left hippocampus (column 4;  $x = -27$ ). (B) Compared to controls, PTSD participants showed greater connectivity between ventromedial prefrontal cortex (vmPFC; seed region shown in B) and supplementary motor area (column 2;  $x = 5$ ) and bilateral superior temporal sulcus (column 3;  $z = 11$ ) and less connectivity between vmPFC seed and rostral anterior cingulate cortex (column 4;  $x = -10$ ). (C) Compared to controls, PTSD participants showed greater connectivity between left anterior insula (=seed region shown in C) and right amygdala (column 2;  $y = 8$ ), left peri-insula (column 3;  $z = 21$ ) and right hippocampus (column 4;  $x = 37$ ).