Supplementary Methods

# Participants

Participants were post-9/11 veteran service members of Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND). Participants in the Center (Translational Research Center of Traumatic Brain Injury and Stress Disorders; TRACTS; McGlinchey et al., 2017) are recruited from the General Boston Metropolitan and the larger New England areas via a full-time recruitment specialist attending local military events. Inclusionary criterion for enrollment in TRACTS was to be aged between 18-65, and had served in OEF/OIF/OND or had a scheduled deployment (96.31% or 261/271 were post-deployment). The trauma experienced by these veterans was heterogenous, arising from various sources and frequency. Exclusion criteria for the TRACTS cohort includes prior serious medical and/or neurological illness unrelated to traumatic brain injury (TBI), active suicidal and/or homicidal ideation requiring intervention, or a current diagnosis of bipolar disorder or psychotic disorder (except psychosis not otherwise specified due to trauma-related hallucinations) according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 2000). Of the initial 307 participants available at the start of this project, 18 were excluded for greater than 20% of functional volumes censored for outstanding motion, 4 for mean functional connectivity that was greater than 3 standard deviations from the group mean, and an additional 14 individuals were removed that failed a performance validity test; thus the following analysis was conducted with 271 subjects. For more information regarding the quality control metrics for neuroimaging (censored volumes and mean functional connectivity outliers) see Image Processing below.

# Assessment of PTSD, comorbidities, and medication use

Symptom clusters of PTSD were assessed by sub-scales provided by the CAPS-IV. The CAPS-IV provides summed scores for the Criterion B (re-experiencing), Criterion C (avoidance and numbing), and Criterion D (hyperarousal) items from the diagnostic interview. Further, we assessed common comorbidities of PTSD, including depression and anxiety (Depression Total Score and Anxiety Total Score from the Depression Anxiety Stress Scales [DASS]; Lovibond & Lovibond, 1995), mild military TBI (Boston Assessment of TBI-Lifetime [BAT-L]; Fortier et al., 2014), average alcohol use (Average Number of Drinks on a Drinking Day from Lifetime Drinking History [LDH]; Skinner & Sheu, 1982), average pain (Average Pain in the Last Month from the McGill Short Form; Melzack & Katz, 2013), and sleep quality (Global Sleep Score from the Pittsburgh Sleep Quality Index [PSQI]; Buysse et al., 1989). Mild military TBI was selected to control for traumatic brain injury, as previous literature has determined that military TBI explained the most variance in cognition (DeGutis et al., 2015; Esterman et al., 2019; Riley et al., 2019). Dichotomized (yes or no) self-report of current medication use included anti-depressant, epileptic, pain, and sedative/hypnotic at the time of assessment.

# Performance Validity

Commonly, practitioners and researchers include a measure of effort to help determine the validity of performance on neuropsychological test(s) (Heilbronner et al., 2009; Iverson, 2005; Stricker et al., 2017). This study used the Medical Symptom Validity Test (MSVT; Green, 2004) to determine validity of performance on neuropsychological tests. The criterion determining effort failure on the MSVT required scoring an 85% or less on immediate recall, delayed recall, or consistency (Clark et al., 2014). Individuals that failed the MSVT (*n*=14) were removed from the analysis, as the validity of their clinical and neuropsychological data was uncertain (Riley et al., 2019).

# Neuropsychological Tests

The executive function composite included the number sequencing switching subtest B from the Trail Making Test (Trails B – Delis-Kaplan Executive Function System [DKEFS]; Delis et al., 2001), Stroop test from the DKEFS (Delis et al., 2001), Intra-Extra Dimensional Set Shift from CANTAB (http://www.cantab.com), verbal fluency from the DKEFS (Delis et al., 2001), and Auditory Consonant Trigrams (Stuss et al., 1985). For all measures, age-adjusted standardized performance *z*-scores were computed.

# Neuroimaging

MRI Acquisition. Two T1-weighted anatomical MPRAGE scans (TR = 2530ms, TE = 3.32ms, flip angle: 7°, 1-mm isotropic) were acquired for inter-participant registration and normalization. Two six-minute T2\* weighted fMRI scans (gradient echo-planar imaging – TR: 3000ms, TE: 30ms, flip angle: 90°, 3x3x3.7 mm slices for 38 slices) were acquired during rest. There were 58 subjects (20.35% of participants) that had a shorter scans duration (two four-minute scans) with shorter TR (2000ms) due to unintended operator variability unrelated to any individual difference. The same number of volumes were collected, regardless of TR (240 volumes total). Scan duration (8 vs. 10 mins) was included as a covariate in follow-up analyses. During rest (resting-state fMRI) participants were instructed to keep their eyes open and stay awake.

Image Processing

Resting-state fMRI images were preprocessed using AFNI (Cox, 1996). This processing pipeline included motion correction, registration to standard space, slice time correction, scan concatenation, censoring of timepoints with a framewise displacement (> 0.5 mm), 6mm FWHM Gaussian smoothing, followed by regression of motion parameters, white matter time series, ventricle time series, global signal, and high-pass filtering via linear, quadratic and cubic detrending. We chose to include global signal regression since it removes motion and respiratory artifacts and previous work suggests that regressing out global signal improves resting-state connectivity/behavior relationships (Li et al., 2019). Control for head motion confounds in resting-state involved removing individuals with greater than 20% of their functional MRI scan censored during preprocessing. Those with mean edge-wise functional connectivity that were greater than 3 standard deviation from the mean were removed (functional connectivity outliers). An additional measure of head motion was calculated, to covary for uncontrolled motion-related artifacts (Power et al., 2011). This head motion (HM) regressor was calculated as the mean absolute displacement of the motion parameters. The timeseries from each voxel went through additional cleaning steps. First, if the mode of the timeseries value at a given voxel composed more than 20% of the values within that voxel, that voxel was removed due to signal loss. Next, for each timeseries, timepoints censored in preprocessing were imputed via linear interpolation. Finally, in order to reduce the influence of extreme values when computing functional connectivity, outliers in each timeseries that were greater than or less than four standard deviations from the mean were reassigned the threshold value (i.e. clipping; McNorgan & Joanisse, 2014). A summary head motion variable (mean absolute displacement of the motion parameters) was computed and used as a covariate in follow up analyses.

Brain Parcellation

The brain was parcellated using a 7-network atlas from Yeo and colleagues (Yeo et al., 2011). This atlas was developed using human resting-state fMRI data, and defines networks commonly discussed in the resting-state literature which improves the interpretability of the functional connectivity results. The volumetric atlas of this space was used, and only nodes (clusters) larger than 25 voxels were retained. A cluster size larger than 25 voxels removed clusters with increased risk for small, idiosyncratic nodes that potentially were artifacts of the transformation to volume space from surface space. This procedure generated 48 cortical ROIs, embedded within the seven large-scale cortical networks. Additionally, the bilateral amygdala and hippocampus from a subcortical, volumetric atlas developed by Tullo and colleagues (Tullo et al., 2018). The networks included the visual network (VN; 2 regions), sensorimotor network (SN; 2 regions), dorsal attention network (DAN; 5 regions), ventral attention network (VAN; 10 regions), limbic network (LN; 4 regions), frontal parietal control network (FPCN; 15 regions), and default mode network (DMN; 10 regions). Additionally, the bilateral amygdala and hippocampus were added to the limbic network (LN) bringing the total number of LN regions to 8. The center of mass, anatomical label and cluster size for each of the ROIs within each of these 7 networks are provided in Supplemental Materials Table 1. The average time series were extracted from each ROI (averaged across the set of voxels within the node) and correlated (Pearson) across nodes for a total of 1,326 pairwise correlations.

Table S1.

Brain Parcellation Anatomical Labels, Center of Mass, and Cluster Size

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Network | Hemisphere | Anatomical Label | Center of Mass | | | Cluster Size |
| Visual Network | Right | Calcarine | 27 | -69 | 3 | 1331 |
| Left | Calcarine | -24 | -75 | 6 | 1155 |
| Sensorimotor Network | Left | Pre/Post Central | -39 | -21 | 36 | 1260 |
| Right | Pre/Post Central | 39 | 18 | 33 | 1272 |
| Dorsal Attention Network | Right | Superior Parietal | 39 | -54 | 30 | 881 |
| Left | Superior Parietal | -36 | -57 | 27 | 817 |
| Left | Frontal Eye Field | -33 | 0 | 48 | 234 |
| Right | Frontal Eye Field | 30 | -3 | 54 | 131 |
| Right | Inferior Frontal | 45 | 6 | 27 | 107 |
| Ventral Attention Network | Right | Insula | 42 | 9 | 0 | 413 |
| Left | Insula | -42 | 6 | 3 | 379 |
| Right | Supplementary Motor | 9 | 0 | 48 | 335 |
| Left | Supplementary Motor | -9 | -3 | 45 | 299 |
| Right | Temporal Parietal | 60 | -33 | 24 | 258 |
| Left | Temporal Parietal | -60 | -33 | 27 | 217 |
| Left | Middle Frontal | -30 | 42 | 30 | 95 |
| Right | Middle Frontal | 30 | 45 | 27 | 70 |
| Left | Middle Temporal | -57 | -57 | 12 | 51 |
| Right | Precentral | 54 | 3 | 45 | 29 |
| Limbic Network | Right | Temporal Pole | 36 | -3 | -33 | 706 |
| Left | Temporal Pole | -36 | -3 | 33 | 679 |
| Left | Orbital Frontal | -12 | 39 | -18 | 403 |
| Right | Orbital Frontal | 12 | 39 | -18 | 376 |
| Right | Amygdala | 24 | -6 | -15 | 56 |
| Left | Amygdala | -21 | -9 | -15 | 60 |
| Right | Hippocampus | 30 | -24 | -12 | 114 |
| Left | Hippocampus | -27 | -24 | -9 | 129 |
| Frontal Parietal Control Network | Right | Dorsolateral Prefrontal | 36 | 36 | 21 | 1069 |
| Left | Dorsolateral Prefrontal | -39 | 36 | 18 | 609 |
| Right | Supramarginal | 48 | -51 | 45 | 238 |
| Left | Supramarginal | -42 | -54 | 48 | 194 |
| Right | Inferior Temporal | 63 | -36 | -15 | 158 |
| Left | Anterior Cingulate | -6 | 18 | 36 | 123 |
| Right | Anterior Cingulate | 6 | 30 | 39 | 136 |
| Left | Inferior Temporal | -60 | -48 | -15 | 129 |
| Right | Precuneus | 6 | -57 | 42 | 98 |
| Left | Orbital Frontal | -27 | 45 | -12 | 72 |
| Left | Superior Frontal | -24 | 9 | 60 | 57 |
| Left | Precuneus | -6 | -72 | 42 | 38 |
| Right | Middle Cingulate | 6 | -12 | 27 | 50 |
| Right | Insula | 33 | 21 | -6 | 36 |
| Left | Insula | -33 | 21 | -6 | 32 |
| Default Mode Network | Left | Ventromedial Prefrontal | -21 | 39 | 18 | 1405 |
| Right | Ventromedial Prefrontal | 21 | 48 | 24 | 849 |
| Left | Middle Temporal | -57 | -18 | -15 | 713 |
| Right | Middle Temporal | 57 | -12 | -18 | 510 |
| Left | Angular | -48 | -63 | 33 | 373 |
| Left | Posterior Cingulate | -6 | -51 | 30 | 327 |
| Right | Angular | 54 | -57 | 27 | 282 |
| Right | Posterior Cingulate | 6 | -51 | 27 | 270 |
| Right | Inferior Frontal | 45 | 30 | -9 | 204 |
| Left | Parahippocampal | -24 | -30 | -18 | 29 |

Table S2.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | LN-FPCN FC | Gender | Age | Edu | WTAR | Mild TBI | Anxiety | Depression | Drink | Sleep | Pain | Scan Duration | Head Motion | Anti-Depressants | Anti-Epileptic | Sedative /Hypnotics | Pain Medication | PTSD Diagnosis | PTSD Symptoms | Att Comp | Mem Comp | Exec Comp | Att Groups | Mem Groups |
| Gender | 0.025 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Age | -0.035 | 0.140\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Edu | 0.017 | 0.118 | 0.344\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WTAR | -0.062 | -0.184\* | 0.053 | 0.154\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mild TBI | 0.094 | -0.136\* | -0.08 | -0.098 | 0.079 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Anxiety | 0.164\* | 0.041 | -0.011 | -0.217\*\* | -0.111 | 0.298\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Depression | 0.162\* | -0.018 | 0.099 | -0.122\* | -0.086 | 0.234\*\* | 0.645\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Drink | 0.042 | -0.215\*\* | -0.144\* | -0.197\* | -0.060 | 0.173\* | 0.265\*\* | 0.194\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sleep | 0.142\* | 0.012 | -0.032 | -0.190\* | -0.088 | 0.344\*\* | 0.547\*\* | 0.459\*\* | 0.321\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pain | 0.164\* | -0.057 | -0.015 | -0.202\* | -0.039 | 0.290\*\* | 0.438\*\* | 0.409\*\* | 0.191\* | 0.428\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scan Duration | -0.023 | -0.077 | -0.029 | 0.003 | 0.065 | 0.135\* | 0.096 | 0.078 | 0.098 | 0.201\* | 0.123 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Head Motion | 0.075 | 0.091 | -0.004 | -0.035 | -0.016\* | 0.014 | 0.073 | 0.045 | 0.097 | 0.000 | -0.101 | 0.098 |  |  |  |  |  |  |  |  |  |  |  |  |
| Anti-Depressants | 0.101 | 0.066 | 0.059 | 0.066 | -0.044 | 0.206 | 0.292\*\* | 0.353\*\* | 0.188\* | 0.336\*\* | 0.245\*\* | 0.195\* | 0.014 |  |  |  |  |  |  |  |  |  |  |  |
| Anti-Epileptic | -0.009 | 0.023 | -0.050 | -0.083 | -0.082\* | 0.095 | 0.061 | 0.087 | 0.168\* | 0.087 | -0.053 | -0.028 | -0.043 | 0.085 |  |  |  |  |  |  |  |  |  |  |
| Sedative/  Hypnotics | 0.050 | -0.040 | -0.056 | -0.028 | 0.053 | 0.130 | 0.252\*\* | 0.165\* | 0.102 | 0.258\* | 0.265\*\* | 0.228\*\* | -0.061 | 0.258\*\* | -0.044 |  |  |  |  |  |  |  |  |  |
| Pain Medication | 0.029 | -0.066 | 0.050 | 0.021 | 0.088\* | 0.008 | 0.135\* | 0.080 | 0.024 | 0.096 | 0.112 | 0.088 | -0.070 | 0.123\* | 0.057 | 0.069 |  |  |  |  |  |  |  |  |
| PTSD Diagnosis | 0.103 | 0.006 | -0.023 | -0.175\* | -0.155\* | 0.348\*\* | 0.476\*\* | 0.504\*\* | 0.226\*\* | 0.572\*\* | 0.339\*\* | 0.171\* | 0.077 | 0.279\*\* | 0.044 | 0.136\* | 0.151\* |  |  |  |  |  |  |  |
| PTSD Symptoms | 0.193\* | 0.069 | -0.040 | -0.183\* | -0.129\* | 0.420\*\* | 0.630\*\* | 0.602\*\* | 0.286\*\* | 0.672\*\* | 0.414\*\* | 0.143\* | 0.059 | 0.327\*\* | 0.100 | 0.204\* | 0.136\* | 0.795\*\* |  |  |  |  |  |  |
| Att Comp | -0.049 | -0.146\* | -0.019 | 0.133\* | 0.295\*\* | -0.038 | -0.069 | -0.066 | -0.127\* | -0.103 | -0.113 | -0.014 | -0.083 | -0.004 | -0.108 | 0.000 | -0.025 | -0.120\* | -0.162\* |  |  |  |  |  |
| Mem Comp | -0.023 | -0.123\* | -0.036 | 0.138\* | 0.210\* | -0.020 | -0.168\* | -0.170\* | -0.099 | -0.154\* | -0.041 | 0.024 | -0.066 | -0.058 | -0.074 | 0.060 | -0.015 | -0.098 | -0.214\*\* | 0.108 |  |  |  |  |
| Exec Comp | -0.055 | -0.094 | -0.013 | 0.188\* | 0.443\*\* | 0.059 | -0.151\* | -0.092 | -0.086 | -0.140\* | -0.146\* | -0.004 | -0.099 | -0.023 | -0.095 | 0.005 | 0.015 | -0.071 | -0.148\* | 0.433\*\* | 0.322\*\* |  |  |  |
| Att Groups | -0.082 | -0.062 | -0.061 | 0.109 | 0.226\*\* | -0.087 | -0.100 | -0.069 | -0.180\* | -0.127\* | -0.088 | -0.095 | 0.009 | -0.069 | -0.113 | -0.038 | -0.047 | -0.144 | -0.168\* | 0.689\*\* | -0.010 | 0.288\*\* |  |  |
| Mem Groups | 0.032 | -0.143\* | 0.039 | 0.096 | 0.220\*\* | 0.000 | -0.118\* | -0.083 | -0.076 | -0.102 | -0.014 | 0.027 | -0.034 | -0.134\* | -0.117 | 0.056 | -0.034 | -0.081 | -0.167\* | 0.051 | 0.746\*\* | 0.298\*\* | -0.048 |  |
| Exec Groups | -0.077 | -0.046 | -0.085 | 0.099 | 0.288\*\* | 0.067 | -0.125 | -0.074 | -0.122 | -0.103 | -0.133\* | 0.048 | 0.007 | 0.002 | -0.056 | 0.012 | -0.006 | -0.011 | -0.096 | 0.362\*\* | 0.201\*\* | 0.693\*\* | 0.222\*\* | 0.182\*\* |

FC = Functional Connectivity, TBI = Traumatic Brain Injury, LN = Limbic network, FPCN = Frontal parietal control network, Att = Attention, Mem = Memory, Exec = Executive, Comp = Composite, \* denotes significant correlation < 0.05, \*\* denotes significant correlation < 0.001, Correlations are Pearson’s correlation, unless the relationship is between a continuous variable and a dichotomous variable (tested via point-biserial correlation), or the relationship is between two dichotomous variables (tested via Phi test of association from Pearson Chi-Square).

Table S3.

Symptom Clusters Correlations, and Linear Models

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Correlations | | | | | |
|  | LN-FPCN | LN-FPCN Semi-Partiala | Re-experiencing | Avoidance and Numbing | Hyperarousal |
| CAPS Total | 0.19\* | 0.20\* |  |  |  |
| Re-experiencing | 0.15\* | 0.15\* | 0.90\*\* |  |  |
| Avoidance and Numbing | 0.19\* | 0.19\* | 0.92\*\* | 0.72\*\* |  |
| Hyperarousal | 0.19\* | 0.19\* | 0.90\*\* | 0.75\*\* | 0.71\*\* |
| Regression Modelsb | | | | | |
| Model | Adjusted R2 | Predictors | | β | p-value |
| Re-experiencing | 0.05\* | Re-experiencing | | 1.12 | <0.001 |
|  |  | EF | | 0.17 | 0.106 |
|  |  | Interaction (Re-experiencing \*EF) | | -0.98 | 0.005 |
| Avoidance and Numbing | 0.05\* | Avoidance and Numbing | | 0.96 | 0.002 |
|  |  | EF | | 0.12 | 0.233 |
|  |  | Interaction (Avoidance and Numbing \*EF) | | -0.77 | 0.026 |
| Hyperarousal | 0.08\*\* | Hyperarousal | | 0.37 | <0.001 |
|  |  | EF | | 1.52 | 0.003 |
|  |  | Interaction (Hyperarousal \*EF) | | -1.35 | <0.001 |

\* and \*\* denotes *p*-value is < 0.05, and < 0.001 respectively. aThe semipartial correlation with covariates age, gender, years of education, and premorbid IQ (WTAR). bAll three regression models include age, gender, years of education and WTAR as covariates.

Supplementary Table 4.

Regression Models

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model | Adjusted R2 | Predictors | β | p-value |
| Primary Model† | 0.07\*\* | PTSD Severity | 1.32 | <0.001 |
|  |  | EF | 0.27 | 0.021 |
|  |  | Interactiona | -1.13 | 0.001 |
|  |  | Age | -0.08 | 0.209 |
|  |  | Gender | 0.01 | 0.874 |
|  |  | Education | 0.07 | 0.265 |
|  |  | WTAR | -0.06 | 0.334 |
| Including | 0.07\* | PTSD Severity | 1.22 | 0.001 |
| Clinical Comorbidities |  | EF | 0.22 | 0.05 |
|  |  | Interactiona | -1.03 | 0.005 |
|  |  | mTBI | 0.04 | 0.591 |
|  |  | Anxiety | 0.07 | 0.424 |
|  |  | Depression | -0.7 | 0.420 |
|  |  | Drink | 0.01 | 0.923 |
|  |  | Sleep | -0.07 | 0.462 |
|  |  | Pain | 0.09 | 0.259 |
| Including | 0.08\*\* | PTSD Severity | 1.299 | <0.001 |
| Scanner Effects |  | EF | 0.26 | 0.02 |
|  |  | Interactiona | -1.10 | 0.001 |
|  |  | Scan Duration | 0.06 | 0.352 |
|  |  | Head Motion | -0.08 | 0.167 |
| Including | 0.07\* | PTSD Severity | 1.23 | <0.001 |
| Medication Use |  | EF | 0.24 | 0.03 |
|  |  | Interactiona | -1.06 | 0.002 |
|  |  | Anti-depressant | 0.06 | 0.383 |
|  |  | Epileptic | -0.01 | 0.875 |
|  |  | Sedative/hypnotic | -0.003 | 0.962 |
|  |  | Pain | -0.04 | 0.537 |

\* denotes significant correlation < 0.05, \*\* denotes significant correlation < 0.001, † denotes that this is the same model reported in the main text, here we provide the standardized beta values for all of the general covariates included in this model to then compare to the follow up analyses.  aThe interaction term indicates the interaction term between PTSD severity and Executive Function (EF).

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