Proposal to ENIGMA-PGC

Connectome-based Neural Network Analyses in Posttraumatic Stress Disorder

Michigan PTSD Connectomics Team

Anthony King, PhD[1, 2]
Yana Lokshina, MS[1]
Chandra Sripada, MD, PhD[1, 3]
Israel Liberzon, MD[1, 2, 4]

[1]Dept. Psychiatry, University of Michigan Medical School, Ann Arbor, MI
[2]VA Ann Arbor Health System, Ann Arbor, MI
[3]Dept. Philosophy, University of Michigan, Ann Arbor, MI
[4]Dept. Psychology, University of Michigan, Ann Arbor, MI

Anthony King, PhD
Assistant Research Professor
Department of Psychiatry
University of Michigan
Ann Arbor, MI 48105
samadhi@med.umich.edu

Abstract:

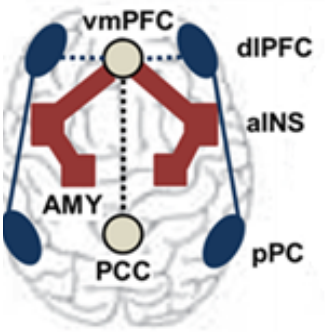
Posttraumatic stress disorder (PTSD) is common and is associated with suffering, disability, and huge human and economic costs to society. Neuroimaging studies over the past 20 years have pointed to potential dysfunction in several brain regions, including amygdala, insula, and frontal cortex, however they have been limited by relatively small N. Furthermore, accumulating evidence converges on the view that neural underpinnings of psychiatric disorders like PTSD may be reflected in dysfunctions in relationships between large-scale, distributed neural networks. Recent advances in resting state functional connectivity (rsFC) methodology have allowed for testing effects psychiatric disorders on large-scale networks, using both a priori "seed" based approaches, as well as unbiased whole brain "connectome-wide" approaches. Evidence from several seed-based rsFC studies suggests PTSD is associated with increased functional connectivity within the Salience Network (associated with detection of salience and threat) and decreased functional connectivity within the Default Mode Network (associated with social cognition and autobiographical memory). Furthermore, PTSD shows aberrantly increased connectivity or "desegregation" between these two networks, which are usually anti-correlated in healthy people. Emerging data from recent *a priori* seed-based and connectome-wide studies also suggest potential contribution of changes in other networks, including attention and cognitive control networks in PTSD. We propose to use the ENIGMA-PTSD sample to conduct the largest confirmatory "mega-analysis" to test *a priori* hypotheses about the role of altered SN and DMN connectivity in PTSD, and to also conduct exploratory analyses using unbiased whole-brain connectomic methodologies to identify potential contributions of additional networks, and elucidate the effects of PTSD on global neural network architecture.

Background: Over 20 years of relatively small neuroimaging studies (SPECT, PET, fMRI) have revealed what appear to be reliable and replicable alterations in several brain regions, including, insula, dmPFC, dorsal ACC, and hippocampus (for reviews and meta-analyses see[1-3]). Mounting evidence from basic, translational, and treatment research converges on the view that neural underpinnings of psychiatric disorders like PTSD may be better understood by dysfunctions in relationships between large-scale neural networks[4-7]. The ENIGMA PGC-PTSD Neuroimaging group offers an unprecedented opportunity to (1) confirm these initial findings and (2) to conduct large N exploratory, well powered studies to identify additional potential targets.

Summary: Thus, our approach will be to conduct (1) confirmatory tests of *a priori* hypotheses regarding the role of desegregation of the Default Mode Network (DMN) and Salience Network (SN), and changes in connectivity within these networks, in PTSD (based upon prior evidence, in the literature described below) using seed-based approaches, and (2) exploratory analyses using connectome-wide approaches to identify potential dysfunction in other networks (e.g., attention and cognitive control networks) and connectivity across the brain at large. We propose to examine "connectomes" integrated over all of resting brain activity (i.e. "static" or averaged connectivity), in accord with the state of the art connectivity studies published in the field over the past decade, including most recent methodological advances. This proposal is a complement to, and is complemented by other proposals under consideration that focus on dynamic connectivity and multimodal classification analysis. With respect to the dynamic connectivity proposal, (i.e. changes in connectivity "states" and metrics of state dwell-time and transitions over the resting epoch), it is yet unknown what approach will yield most informative findings, whether these will be additive or overlapping, and even methodologically it will be highly valuable to compare PTSD findings from both approaches. In relationship to the proposal to use multi-modal MRI measures (including metrics of cortical thickness, subcortical volumetrics, diffusor tension imaging (DTI), and resting state connectivity) as features in machine-learning classification, our proposed analysis is focused only on, but is also far more comprehensive re: rs fMRI analytics. It will produce complementary metrics of integrated network connectivity that can be used in subsequent machine-learning classification studies proposed. This parallel processing analytic approach will thereby greatly increase efficiency and collaboration between ENIGMA-PTSD member groups. Below we briefly describe scientific rational and the specific methods of our proposal.

Large-Scale ICNs in Trauma-related Psychopathology Resting state functional connectivity (rsFC) analyses have identified multiple large-scale intrinsic connectivity networks (ICNs), that correspond to task-related connectivity patterns[8,9]. Over the past 5-7 years, several research groups, including ours, have reported ICN seed-based studies showing individuals with PTSD have hyper-connectivity within the nodes of Salience Network (SN) linked to detection of threat, salience and integration of interoceptive, and emotional information, like insula, dorsal anterior cingulate (dACC) and in some models, amygdala[10-13], Several seed-based studies have also reported decreased within-network connectivity in the "task-negative" Default Mode Network (DMN, linked to self-referential processing, autobiographical memory, and "mind wandering": posterior cingulate cortex (PCC), ventral medial PFC (vmPFC) / subgenual PFC (sgPFC), and hippocampus[12-17] .Finally, PTSD has been associated with aberrantly increased DMN-SN (e.g. DMN-amygdala and insula) cross-network connectivity i.e. network desegregation[12,15,18]. We have previously hypothesized increased DMN-SN connectivity at rest as potentially underlying PTSD hyperarousal symptoms, associated with intrusive, automatic distress reactions to both external cues and internal physiological states.

A few seed-based studies also reported that other ICNs may also contribute to PTSD pathophysiology. Hypervigilance and concentration problems in PTSD involve inappropriate attention to threat and distractibility, which could involve aberrant cross-network hyperconnectivity between Dorsal Attention Network (DAN, involved in voluntary deployment of attention and externally-directed cognitions) and Ventral Attention Network (VAN, involved in reorientation to unexpected events) with DMN and/or SN[19,20]. Recent studies also suggest PTSD related dysfunction in Frontal-Parietal Control Network (FPCN, executive functions and "top-down" control emotional regulation) including impaired modulation of DMN by FPCN[21-23] and FPCN-SN hyperconnectivity[18], consistent with long-standing evidence of dysfunction in frontal cortex and "top-down" inhibitory processing and emotional regulation in PTSD.



A schematic model of dysregulation of large-scale networks in PTSD. DMN is represented by grey circles, SN by red squares, and FPCN by blue ovals. PTSD is associated with increased SN connectivity (represented by thick red lines between amygdala and insula), decreased DMN connectivity (dotted lines between vmPFC and PCC), and aberrantly increased SN-DMN (thick red line between insula and vmPFC). Decreased connectivity between FPCN and DMN is represented by dotted line between dlPFC and vmPFC.

Thus while a reasonably circumscribed set of findings had been emerging from seed based connectivity studies, not all of the hypotheses were replicated by all the studies, ***and large N definitive study is needed to identify these findings that are reliably replicable in the majority of PTSD patients***.

In addition to seed-based analyses, connectome-wide studies using graph theory analysis suggest PTSD-related alterations in the global architecture of brain connectivity. For example, decreased "small-world" topology, consistent with a failure of equilibrium between functional segregation and integration processes in PTSD[26,27] However, PTSD small-world findings to date are mixed[28,29] as are reports of PTSD alterations in clustering coefficient[28,30]. We also present preliminary connectomic data utilizing joint Independent Components Analysis (King, Block, Sripada, & Liberzon, unpublished data) that finds PTSD associated with altered expression of large-scale components of connectivity characterized by increased desegregation (aberrantly increased connectivity) between DMN, DAN, and VAN (see preliminary data below). ***Clearly, well powered studies are required to test these global connectivity findings.***

Hypotheses: Based upon previous work from the Michigan group[10,12,20,23] and others[11,13,15,16,18,21,22], we propose two overarching hypotheses to be tested:

H1. PTSD is associated with Increased within-network connectivity in the Salience Network; decreased within-network connectivity in the Default Mode Network; and increased between-network connectivity (desegregation) between the Salience Network and Default Mode Network

H2: PTSD is associated with altered connectivity across the whole brain and also in attention and cognitive control networks, including increased connectivity between DAN and DMN, DAN and SN, and decreased connectivity between FPCN and DMN

Specific Aims: To test our primary hypotheses, we propose the following Specific Aims:

Aim 1: Confirmatory Seed-based Analyses will be used to test a priori PTSD connectivity hypotheses regarding SN and DMN in seed-based analyses utilizing canonical seed ROIs within critical nodes of relevant ICNs (SN: dorsal ACC, insula, DMN: PCC, vmPFC, hippocampus).

1a. Seed-to-voxel analyses testing whole-brain functional connectivity to canonical seed ROIs.

1b. ROI-to-ROI network analyses testing connectivity between *a priori* DMN and SN nodes.

Aim 2. **Exploratory Whole-Connectome Analyses** We will utilize three complementary approaches based on analyses of "connectomes" (i.e., all pairwise connections between all "nodes" encompassing the entire brain) to identify network abnormalities associated with PTSD in an unbiased, whole-brain level of analysis at three levels of analysis: testing at the level of (a) individual "edges" between connectome nodes, (b) large scale components of connectivity, and (c) global network characteristics.

2a. Connectome-based Modeling will be used to identify specific sets of individual edges within connectomes that are statistically different between PTSD and healthy controls using whole-brain statistical thresholding, and categorize them by canonical networks.

2b. Joint Independent Components Analyses (jICA) will be used to identify PTSD-related differences in large-scale components of connectivity networks. jICA will reveal individual-level distributed network components of connectivity (both within and between canonical ICN networks) that show cohesive patterns of variability between individuals, and allow us to identify effects of PTSD on network components in group-level comparisons.

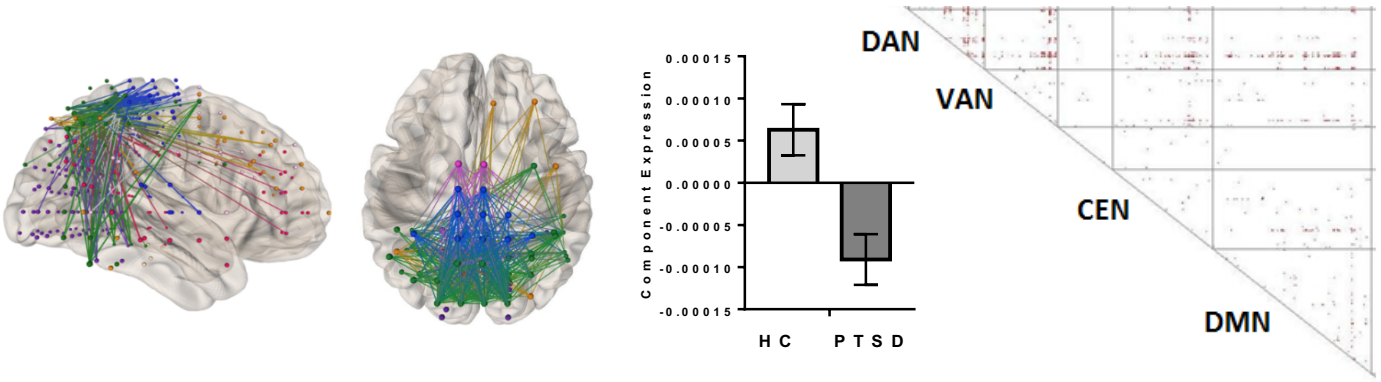
2c. Graph theory analyses will be used to identify PTSD-related alterations in global topological properties of neural networks, including functional segregation and integration (e.g., metrics of global efficiency, small-worldness, modularity, etc.)

Preliminary Data:

We have preliminary seed-based and connectome-based analyses from three medium-sized studies with 3T fMRI resting state data (total of N=147 OEF/OIF combat veterans with and without PTSD and N=40 healthy community controls): (1) a locally funded PTSD fMRI study (PI Israel Liberzon, MD, co-PI Anthony King, PhD) with N=15 OEF/OIF combat PTSD, and N=14 OEF/OIF combat healthy controls, (2) PTSD Mindfulness-based Exposure Therapy study (W81XWH-08-2-0208, PI: Israel Liberzon, MD; co-PI Anthony King, PhD) with N=39 OEF/OIF combat PTSD patients and N=26 healthy controls, and the PROgRESS study (W81XWH-11-1-0073,

coordinating PI: Sheila Rauch, PhD, fMRI PI: Israel Liberzon, MD) with N=69 OEF/OIF combat PTSD and N=29 OEF/OIF combat healthy controls.

Connectomic Analysis reveals PTSD associated with altered expression of a connectivity component comprised of negative connectivity (segregation) between DMN, DAN, and VAN.



Joint ICA of N=32 OEF/OIF PTSD and N=26 healthy controls: PTSD Associated with Desegregation of DMN and DAN and VAN. "Connectomes" were generated from Pearson correlations of spatially-averaged time-series of all pair-wise combination of 1068 regions of interest (ROIs) in a 12 mm grid spanning the whole brain. Connectome data were decomposed into 15 spatial components using joint Independent Components Analysis (jICA) and ordered into categories of ICNs (e.g. DMN, SN, DAN, FPCN/ CEN, etc.). Expression of a joint ICA "parietal" independent component (IC) was significantly decreased in PTSD compared to healthy controls ($t(48.4) = 3.6$, $p = 0.0008$). This parietal IC was expressed medially and bilaterally and was composed of negative cross-network connectivity of the DAN and VAN to DMN; consistent with PTSD showing relative desegregation between DMN, DAN, and VAN. Expression of this IC was associated with a behavioral measure, mean response time (RT) in the Attention Network Task (ANT) $t(51) = -2.1378$, $p = 0.04$ (PTSD had lower expression of the parietal IC and higher RT (slower responses) in the ANT).

Analysis Plan:

Participants: We will utilize resting state fMRI scans and clinical and demographic metadata collected by the ENIGMA-PGC PTSD consortium from ~3000 participants; approximately N=1500 with current PTSD diagnosis, and N=1500 healthy people who have been exposed to trauma but no current or lifetime history of PTSD. PTSD diagnosis and severity and demographics will be obtained from individual studies; the majority of studies use CAPS to assess PTSD, covariates will be harmonized across studies as necessary. Participants will be excluded if they have lifetime diagnosis of schizophrenia, bipolar disorder, or other psychotic disorder, significant cognitive disability, or neurological disorders. Participants with organic brain damage due to traumatic brain injury will be excluded, but mild TBI / post-concussive syndrome will be allowed but coded as a co-variable. Presence of major depression will be allowed in PTSD patients but not healthy controls but will be coded as a covariable in analyses. Other covariables of interest will include childhood maltreatment / adversity and adult trauma exposure categories, harmonized across studies.

MRI Data Acquisition, pre-processing, and artifact removal. Resting state raw fMRI data contributed from all sites will be pre-processed using the standardized multisite ENIGMA pipeline to process resting state scans in a harmonized manner. We will use the single-modality ENIGMA rsfMRI preprocessing pipeline (recently reported in Adhikari et al., 2018)[24] utilizing model-free Marchenko-Pastur PCA based de-noising, and which will apply standard preprocessing steps (e.g. spatial distortion removal, realignment, co-registration, warping to MNI space). Standard artifact removal will involve linear detrending and regression applied to each voxel's time series to remove nuisance effects. Regressors will include the top five PCs from PCA of BOLD time series from cerebrospinal fluid and white matter masks (to remove signal from cardiac and respiratory cycles, and the time-series band- pass filtered in the 0.01 – 0.10 Hz range, and motion terms (from realignment), their first derivatives and quadratic terms (to reduce motion artifact). Each methodological approach also includes methods for removing motion artifact, which is particularly important for rs fMRI analyses. To reduce motion artifact that can confound connectivity measures, we will apply "Motion Scrubbing" (censoring of individual frames from the time series). We will initially set the framewise displacement threshold for excessive motion to 0.2 mm; subjects with more than 33% of frames removed by scrubbing will be excluded.

Aim 1. Confirmatory Seed-based Approaches. To test a priori hypotheses regarding DMN and SN connectivity, we will test "seed-to-voxel" and ROI-to-ROI network connectivity analyses of the CONN toolbox utilizing previously validated a priori "seed" ROIs from canonical nodes in DMN (PCC, vmPFC, bilateral hippocampus) and SN (bilateral insula, dorsal ACC, bilateral amygdala), and whole-brain statistical thresholding (FDR). The models will be controlled for nuisance variables (e.g. site, length of scan, etc.) and the potential influence of covariates of interest including sex, age, childhood trauma / adversity, adult trauma load, mild TBI, depression co-morbidity, etc. will also be tested and controlled for in models of PTSD.

Aim 2 Exploratory Connectome-based Approaches to test whole-brain connectome-wide hypotheses:

Connectome generation. We will have produce a whole-brain resting state functional connectome as wehave previously reported[32,33], placing ROIs encompassing nineteen 3 x 3 x 3 mm voxels in a regular grid spaced at 12 mm intervals throughout the brain, yielding 1080 ROIs in total. We will utilize the network parcellation of Yeo et al., 2011[9], which included convergent methods to test reliability and parcellation using grid-based connectomic methods similar to current study. Spatially averaged time series will be extracted from each of ROIs followed by regression to remove nuisance effects. Pearson's correlation coefficients will be calculated pairwise between time courses for each ROI, producing a cross-correlation map with ~500,000 non-redundant entries, and Fisher's r-z-transformation is applied for subsequent statistical analysis, as we have previously reported[32,33,34,35]

2a. Connectome-based Tests. All edges in connectivity matrices of generated connectomes will be regressed to the group variable (PTSD diagnosis or severity), and a whole-brain significance threshold applied to select the PTSD-related edges[36]. Contrasts will be applied to detect group differences in functional connectivity, two-tailed t tests on the values of each cell to create a "difference matrix" of t scores representing the magnitude of group difference at each edge. We then will threshold the matrix and apply multiple comparison corrections using network-based statistics (NBS)[37], in which the largest fully connected network of suprathreshold edges, or "component," is identified, and its extent is defined as the number of edges it comprises. Group assignments of subjects will be randomly permuted (10,000 permutations) to create a null distribution for the expected component size due to chance[36]. The data generated from these analyses can also be used in predictive modeling of PTSD; i.e., selected edges can be summarized to a per subject single value, and a predictive model built that classifies a set of edges to a diagnostic group. Summary values calculated for each subject in the testing set will be input to predictive model, and cross-validation (e.g. leave-one-out, k-fold cross validation) can be applied.

2b. Joint Independent Components Analysis (jICA). We will identify patterns of inter-individual variation across the connectome as we have reported previously using jICA[32,33,34,35] to identify independent components (ICs) that exhibit cohesive patterns of variation across subjects. "ICA-Fix" will reduce movement noise regressing 24 movement parameters (6 parameter time series, temporal derivatives, and squares). We will use GIFT toolbox, mialab.mrn.org/ software/gift/) for jICA and empirically choose models (e.g. 10-20 ICs) to best represent brain areas of networks of interest (DMN, FPCN, etc) without over-parcellation. Time courses will be a matrix of N volumes x k ICs, and will be post-processed using GIFT toolbox: lowpass filtering (0.15 Hz), detrending, and "despiking" (AFNI 3dDespike algorithm replaces data points larger than median deviation with a spline fit; similar to "data scrubbing" but does not disrupt temporal continuity. Pearson correlations will be calculated between ICs using the processed data, resulting in functional connections that will be fit in an IC correlation matrix ordered into networks (DMN, SN etc.), and individual variability will be back-projected to test PTSD-related differences in strength of derived connectivity networks in between-subjects analyses.

2c. Graph Theory metrics. We will utilize graph theory algorithms to calculate both global (small-worldness, global efficiency, strength, modularity) and local network metrics (local efficiency, node degree and betweenness centrality) from individual-level connectomes[38,39]. Because networks of individual subjects differ in the number of edges, we will employ sparsity thresholds (S) to the correlation matrices to provide each graph (network) with the same number of edges[39], defined as the fraction of the total number of edges remaining in a network. We will utilize threshold strategies to produces networks that could estimate small-worldness with sparse properties and the minimum possible number of spurious edges. We will calculate area under the curve (AUC) for each network metric (over the sparsity range of thresholds) as a summarized scalar for the topological characterization of neural networks[38,39], and will utilize nonparametric permutation tests to identify significant between-group differences in the AUCs of all of the graph metrics (e.g. network efficiency, small-world properties and nodal characteristics) of the generated functional connectomes between the PTSD patients and healthy control subjects.

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