PROPOSAL
for
ENIGMA-PGC PTSD

Resting State Functional Connectivity of the Default Mode Network Subsystems in PTSD

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Abstract

Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterized by debilitating re-experiencing, avoidance, and hyperarousal symptoms following trauma exposure. Recent evidence suggests that individuals with PTSD show disrupted functional connectivity in the default mode network, an intrinsic network that consists of a midline core, a medial temporal lobe (MTL) subsystem, and a dorsomedial prefrontal cortex (dMPFC) subsystem. Although there is a lot of work investigating the default mode network in PTSD, there is not much research focused on the default mode network subsystems in PTSD. Therefore, a large study investigating whether functional connectivity in these subsystems is differentially disrupted in PTSD is needed to better understand the role of the default mode network in the disorder. Here, we propose to use a seed-based approach in the ENIGMA-PGC PTSD sample of ~1500 PTSD patients and ~1500 controls to examine resting state functional connectivity in the default mode network subsystems in PTSD.

A. Research Question, Goal, or Specific Aims
Provide a brief description (e.g., 1 paragraph) describing the aims of the proposal and the research questions to be addressed.

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder that develops after exposure to highly distressing and life-threatening events. The most common features of PTSD include re-experiencing of the trauma (e.g. flashbacks), avoidance (e.g., avoiding trauma-related stimuli or trauma-evoking situations), and hyperarousal symptoms (e.g., hypervigilance). Current neurocircuitry models of PTSD suggest that the medial prefrontal cortex and hippocampus are critically involved in mediating the disorder (1-7). According to these models, abnormal structure and function of the ventromedial prefrontal cortex (vMPFC) in PTSD results in a failure to regulate activity in brain regions important for fear expression and appraisal, leading to an exaggerated fear response (3, 4, 8-13). Further, alterations in hippocampal function in PTSD may contribute to impaired contextual fear learning (3, 4, 9, 10) and impaired contextual fear extinction recall (11, 14, 15), an adaptive process that relies on both the hippocampus and vMPFC (16-19). Taken together, these studies suggest that PTSD is associated with dysregulation of a frontal-medial temporal lobe (MTL) circuit that results in an exaggerated fear response and an inability to extinguish this fear when the context no longer predicts threat.

More recently, studies have used resting state functional MRI (rs-fMRI) to examine connectivity among brain regions that form integrated networks in PTSD. One such network is the default mode network, which includes the MTL, posterior cingulate cortex (PCC), medial prefrontal cortex, inferior parietal lobule, and lateral temporal cortex (20). Several studies have found PTSD-related alterations in the default mode network (21-26), and a recent meta-analysis found that PTSD is consistently associated with *reduced* functional connectivity (27). Evidence in healthy individuals suggests that the default mode network can be further fractionated into a midline core consisting of the PCC and anterior medial prefrontal cortex (aMPFC) and two functionally and anatomically distinct subsystems (28): a MTL system that includes the vMPFC, posterior inferior parietal lobule, retrosplenial cortex, parahippocampal cortex, and hippocampal formation; and a dorsomedial prefrontal cortex (dMPFC) system that includes the dMPFC, temporoparietal junction, lateral temporal cortex, and temporal pole. These subsystems are differentially affected by MTL lesions (29) and are thought to be involved in distinct cognitive processes (28, 30). For example, the MTL subsystem includes regions that are important for learning and memory (30), while the dMPFC subsystem includes regions that are critical for mentalizing and social processing of the self and others (30-32). Although there is evidence that connectivity within the default mode network is compromised in PTSD (21-25, 27, 33), it is unclear whether the subsystems of the default mode network are differentially disrupted. As memory alterations appear to be a core feature of the disorder (34, 35), we predict that the MTL subsystem might be particularly affected in PTSD.

In addition to disruptions to the default mode network, other networks are also altered in PTSD (23, 25, 27, 36). Networks such as the salience network and central executive network are engaged during externally-directed and attention-demanding tasks and are anticorrelated with the default mode network. Daniels et al. (36) found that individuals with PTSD may have difficulty disengaging the default mode network and engaging salience and central executive networks during attention-demanding tasks. Further, there appears to be increased cross-network connectivity between the default mode network and salience network in PTSD at rest (23, 27), which suggests that neural networks may be less differentiated in PTSD.

In our previous work (37), we examined whether functional connectivity in the default mode network subsystems was differentially disrupted in a cohort of 69 veterans with PTSD compared to 44 trauma-exposed veterans without PTSD. We found selective alterations in functional connectivity in the MTL subsystem of the default mode network in PTSD, with

reduced correlation between the PCC and the hippocampus and reduced anticorrelation between the vMPFC and the dorsal anterior cingulate cortex. Further, we found that functional connectivity between the PCC and hippocampus was associated with avoidance/numbing symptoms (i.e., avoidance of thoughts and feelings associated with the trauma, avoidance of reminders of the trauma, or inability to recall an important aspect of the trauma), such that PTSD individuals with reduced PCC-hippocampal functional connectivity exhibited more symptoms. In contrast, no alterations were observed in the dMPFC subsystem of the default mode network. Although this work is a good first step in further understanding the role of the default mode network in PTSD, more research is needed to confirm these initial findings. The ENIGMA PGC-PTSD neuroimaging group offers an unprecedented opportunity to do so in a large sample. Moreover, PTSD and depression were highly comorbid in our original sample, raising a question concerning the specificity of our findings. Complicating this question, PTSD encompasses an array of symptoms, some shared with depression and some unique. Thus, the ENIGMA PGC-PTSD neuroimaging group also offers an opportunity to investigate the specificity of these initial findings by including depression as a variable of interest.

The objective of this study is to use seed based resting state functional magnetic resonance imaging (rs-fMRI) in a large cohort to examine how PTSD affects the default mode network subsystems. Given the critical role of the vMPFC and hippocampus in PTSD, two areas associated with the MTL subsystem of the default mode network, as well as our initial findings, we hypothesize that PTSD will be associated with decreased default mode network functional connectivity specific to the MTL subsystem. Additionally, in light of evidence for diminished network segregation in PTSD (23, 27, 37), we hypothesize that PTSD will be associated with increased connectivity (i.e., reduced anticorrelation) between the default mode network and regions outside of the default mode network, such as those in the salience and central executive networks. Lastly, we hypothesize that MTL subsystem disruptions will be specific to PTSD when accounting for depression.

B. Analyses Plan

Primary Aim

To use seed based resting state functional magnetic resonance imaging (rs-fMRI) in a large cohort to examine how PTSD affects the default mode network subsystems.

Primary Hypotheses

1. We hypothesize that PTSD will be associated with decreased default mode network functional connectivity specific to the MTL subsystem.
2. We hypothesize that PTSD will be associated with increased connectivity (i.e., reduced anticorrelation) between the default mode network and regions outside of the default mode network, such as those in the salience and central executive networks.
3. We hypothesize that MTL subsystem disruptions will be specific to PTSD when accounting for depression.

Variables to be used in the analysis (the main predictor and outcome variables, and potential covariates must be identified)

Main predictor

- Diagnosis (PTSD vs healthy controls)
- PTSD symptom severity (including symptom subscores)

- For depression sub analysis- depression diagnosis (comorbid depression PTSD, PTSD only, depression only, controls)

Outcome variables

- DMN subsystem functional connectivity
    - Hubs of core network (PCC and aMPFC)
    - Hub of dorsal medial prefrontal cortex subsystem (dMPFC)
    - Hub of medial temporal lob sybsystem (vMPFC)

Covariates

- Age
- Gender
- Depression (yes/no)
- mTBI (yes/no)
- Scanner

Age^2

PTSD x Age

Childhood Trauma (number of categories from CTQ)

PTSD x Childhood Trauma

Gender

ICV

Comorbidity (depression and alcohol use disorder)

Some of the thalamic nuclei defined by Iglesias and colleagues are very small. To minimize floor effects and segmentation failures, we recombine these subnuclei to five larger groups of thalamic subnuclei per hemisphere (see table below).

Participants

Eligible participants will be accessed through the ENIGMA-PGC PTSD consortium. Resting state scans are estimated to include ~1500 PTSD patients and ~1500 controls. PTSD diagnosis will be obtained from individual studies and was assessed with the Clinician-Administered PTSD Scale (CAPS), the PTSD Symptom Scale (PSS), or equivalent. Exclusionary criteria will include (a) past or current Axis I disorders other than PTSD or MDD, (b) current substance disorder, (c) history of moderate or severe TBI, and/or (d) history of a significant neurological condition (e.g., stroke).

Resting State fMRI Analyses

Preprocessing. Resting state data will be analyzed centrally and preprocessed using the ENIGMA resting-state pipeline (38). First, we will use Marchenko-Pastur principal components analysis for denoising to improve the signal-to-noise ratio of the data. Next, we will correct for spatial distortion associated with long-TE gradient echo imaging (i.e., using gradient-echo fieldmap or reversed-gradient approach). Third, we will compute a transformation by registering the base volume to the ENIGMA EPI template to develop a spatial template and spatial atlas, which will be used for regression of the global signal and an anatomical spatial reference frame. Correction for head motion will then be performed by registering each volume

to the volume with the minimum outlier fraction. Nuisance variables including linear trend, the 6 motion parameters and their derivatives, and the time courses of white matter and cerebrospinal fluid (CSF) from the lateral ventricles will be modelled in multiple linear regression analyses. Time points of excessive motion (>0.2mm) will be further censored from the analyses. Images will be spatially normalized to the ENIGMA EPI template in MNI standard space and smoothed for group-level analyses.

First-level processing. Whole-brain resting-state fMRI analyses will be performed using a seed based approach. Seeds will consist of four 8-mm spherical regions of interest (ROIS) obtained from Andrews-Hanna et al. (28): PCC (MNI coordinates = -8, -56, 26), aMPFC (MNI coordinates = -6, 52, -2), dMPFC (MNI coordinates = 0, 52, 26), and vMPFC (MNI coordinates = 0, 26, -18). The PCC and aMPFC seeds were chosen because they represent the two core hubs of the default mode network; the dMPFC and vMPFC seeds were selected because they represent the core hubs of the dMPFC and MTL subsystems, respectively. All seeds and ROIs of CSF, white matter, and whole brain will be first transformed to each individual's native space and then the mean time series (based on all of the voxels within the region) will be computed. Next, we will complete a whole-brain voxel-wise analysis assessing the correlation between the seed region and the rest of the brain, with nuisance regressors (CSF, white matter, and whole brain time-series along with the motion parameters) included in the model.

Group-level processing. To determine connectivity differences across groups (PTSD v. controls), group level connectivity maps will be generated for each seed. Age, sex, depression (yes/no), mTBI (yes/no), and scanner site will be entered into the model as covariates. Statistic images will be thresholded using clusters determined by $p<0.001$ with a corrected cluster significance threshold of $p=0.05$.

To examine associations between functional connectivity and PTSD symptom sub-scores, *Z*-values of significant functional connectivity clusters in the group contrast will be extracted from connectivity maps and entered into SPSS. For the subset of participants that have more detailed information regarding PTSD including PTSD symptom sub-scores, Pearson correlations will be calculated between functional connectivity *Z*-values and CAPS re-experiencing, avoidance/numbing, and hyperarousal scores. Bonferroni correction will be used to correct for multiple comparisons.

To determine whether the observed PTSD alterations could be linked specifically to PTSD rather than depression, additional analyses will be limited to participants with depression information and groups will be further divided into comorbid depression and PTSD, PTSD only, depression only, and controls. Group level connectivity maps will be generated for each seed. Age, sex, mTBI (yes/no), and scanner site will be entered into the model as covariates. Statistic images will be thresholded using clusters determined by $p<0.001$ with a corrected cluster significance threshold of $p=0.05$.

C. Investigative Team

1. Danielle Sullivan
2. Jasmeet Hayes
3. Mieke Verfaellie
4. Mark Miller
5. Erika Wolf
6. Mark Logue
7. David Salat

D. Resources Needed

Describe the resources needed to achieve the aims of the analysis, including variables needed, analysis support, and any other issues that may affect the feasibility of the plan.

Resting state data will be analyzed centrally and preprocessed using the ENIGMA resting-state pipeline using FSL's FEAT program. Whole-brain resting-state fMRI analyses will be performed using a seed based approach. Seeds will consist of four 8-mm spherical regions of interest (ROIS) obtained from Andrews-Hanna et al. (28): PCC (MNI coordinates = -8, -56, 26), aMPFC (MNI coordinates = -6, 52, -2), dMPFC (MNI coordinates = 0, 52, 26), and vMPFC (MNI coordinates = 0, 26, -18). All seeds and ROIs of CSF, white matter, and whole brain will be first transformed to each individual's native space and then the mean time series (based on all of the voxels within the region) will be computed. Next, we will complete a whole-brain voxel-wise analysis assessing the correlation between the seed region and the rest of the brain, with nuisance regressors (CSF, white matter, and whole brain time-series along with the motion parameters) included in the model. Then, group level connectivity maps will be generated examining our variable of interest along with covariates.

E. Timeline

6 months

F. Collaboration

The following is the standard PGC policy about secondary analyses. Any deviation from this policy needs to be described and justified, and could negatively impact the proposal.
PGC investigators who are not named on this proposal but who wish to substantively contribute to the analysis and manuscript may contact the proposing group to discuss joining the proposal.

G. Authorship

We will follow the authorship policy of the PGC-PTSD which can be found at https://pgc-ptsd.com/wp-content/uploads/2017/06/Authorship-Guidelines-PGC-PTSD.pdf

(a) are you following the authorship policies of the groups involved? YES see https://pgc-ptsd.com/wp-content/uploads/2017/06/Authorship-Guidelines-PGC-PTSD.pdf
(b) will there be a writing group and if so, who will be included? The writing group will be comprised of the investigative team (#1 - #5) listed above.
(c) what groups or individuals will be listed as authors? Authors will include the writing group plus individual and group contributors of data and analysis from each site (generally 2-3 co-authors from each site).
(d) will PGC members not listed as named authors be listed at the end of the manuscript? All individuals who meet the criteria established in the PGC-PTSD authorship policy will be co-authors. Other PGC members will not be listed at the end of the manuscript.
(e) will PGC members or groups be listed as "collaborators" on the PubMed abstract page? All individuals and groups who meet the authorship criteria of the PGC-PTSD authorship policy will be listed as collaborators on the PubMed abstract page. No other individuals or groups will be listed.
(f) how will funding sources be handled or acknowledged? All funding sources that supported data collection and analysis will be listed in the manuscript.

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