PROPOSAL

for

ENIGMA-PGC PTSD

Dynamic Resting-State Functional Connectivity in Posttraumatic Stress Disorder

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Abstract (<150 words)

Posttraumatic stress disorder (PTSD) is associated with abnormal static resting-state functional connectivity (rsFC), especially in amygdala, hippocampus, anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC). However, little is known about PTSD-related dynamic changes in functional connectivity. We hypothesize that patients with PTSD is associated with reduced temporal variability of functional connectivity than trauma-exposed controls based on compromised abilities of PTSD patients to dynamically adjust behaviors and thoughts to changing conditions and a preoccupation with trauma-related experiences. We will compare patients with PTSD (N~=1500) to trauma-exposed controls (N~=1500) from ENIGMA-PGC PTSD project on dynamic rsFC based on the standard deviations in rsFC of amygdala, hippocampus and mPFC over a series of sliding windows. The proposed research may advance knowledges of fluctuating communications among brain systems in PTSD.

Keywords: Dynamic Functional Connectivity; Resting-State fMRI; PTSD; amygdala; hippocampus; mPFC.

Background:

Posttraumatic Stress Disorder (PTSD) is a mental health problem that some people develop after experiencing or witnessing a life-threatening event, like combat, a natural disaster, a car accident, or sexual assault (Shalev *et al*, 2017). Previous studies have documented several PTSD-related brain areas including amygdala, hippocampus, medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC) and insula (Brown *et al*, 2014; Morey *et al*, 2012; Morey *et al*, 2016), that are associated with emotion, memory and executive functions (Shalev *et al*, 2017). The methodological development in resting-state functional magnetic resonance imaging (fMRI) method makes it straightforward to compare brain activity across groups without relying on task demands and instructions, whereas functional connectivity is a common analysis for resting-state fMRI data and refers to measures of correlation between pairs of fMRI time series obtained from different brain regions (Lee *et al*, 2013; van den Heuvel and Pol, 2010). Previous studies showed that PTSD is associated with larger resting-state functional connectivity (rsFC) between amygdala and insula (Rabinak *et al*, 2011), smaller amygdala-hippocampus rsFC (Sripada *et al*, 2012), and larger amygdala-ACC/dorsal mPFC rsFC (Brown *et al*, 2014). A recent review reported increased rsFC in salience network but decreased rsFC in default mode network in PTSD (Koch *et al*, 2016).

Most of rsFC studies on PTSD utilized the static functional connectivity method, which assumes that functional connectivity between regions is stationary over time (Koch *et al*, 2016). However, static rsFC outputs only one connectivity value per voxel during the entire length of the scan, and potentially leads to loss of information and sensitivity to the underlying dynamic neural processes (Allen *et al*, 2014). By contrast, nonstationary and spontaneous relationships exist in rsFC regardless of conscious cognitive processing (Hutchison *et al*, 2013). Further, dynamic variations in rsFC are relevant to changes in vigilance (Thompson *et al*, 2013), arousal (Chang *et al*, 2013), emotional state (Cribben *et al*, 2012), and behavioral performance (Jia *et al*, 2014). A recent study by Jin *et al* (2017) showed that patients with PTSD were associated with stronger static but weaker dynamic rsFC, suggesting compromised abilities in PTSD patients to dynamically adjust behaviors and thoughts to changing conditions. The decreased dynamic rsFC has also been detected in other psychiatric disorders (Sakoglu *et al*, 2010), and was found to relate with compromised behavioral performance in healthy controls (Jia *et al*, 2014). Interestingly, dynamic rsFC exhibited higher accuracy than static rsFC in differentiating PTSD from trauma-exposed controls with machine learning (Jin *et al*, 2017).

Unfortunately, to the best of our knowledge, there is only one study by Jin *et al* (2017) investigating dynamic rsFC in patients with PTSD among Chinese earthquake survivors. The sample size in their study is also relatively small (N < 100 per group). Little is known about whether their findings could be generalized to a larger sample size with participants of diverse trauma types. Moreover, it is still unclear how rsFC is affected between areas important to PTSD, including amygdala, hippocampus, ACC and mPFC. By expanding our investigation into a larger sample size (N~=1,500 per group) with participants from diverse sites and accompanied with different trauma types, we may delineate the dynamic functional connections between areas in PTSD without the bias of trauma type and demographic information. The knowledge gained may contribute to advancing our understanding of the neurobiology of PTSD and in future may shed light on treatments for PTSD.

Specific Aims and Objectives:

Aim: Investigate Dynamic rsFC in PTSD. Diagnosis of PTSD will be performed with the Clinician Administration PTSD Scale (CAPS). Measures of brain activity from resting-state functional MRI scans, obtained from the ENIGMA-PTSD project proposed in this application, will be analyzed for dynamic rsFC. Given the compromised abilities of PTSD patients to dynamically

adjust behaviors and thoughts to changing conditions and a preoccupation with trauma-related experiences, we hypothesize that PTSD patients compared to trauma-exposed controls will be associated with reduced dynamic rsFC between important seed areas, including amygdala, hippocampus, ACC and mPFC, and the rest of the brain.

Research Plan:

Participants: We will target PTSD patients from the ENIGMA-PTSD project to achieve detailed clinical measures including PTSD scores. The sample size of N~=1500 per group will provide excellent power to make inferences about brain dynamic rsFC associated with differences between PTSD patients and trauma-exposed controls. We will exclude all participants with Axis I disorders except those with PTSD, major depression, and past substance abuse. We will exclude participants with significant neurological disorders (e.g. seizure, stroke), major neurological surgery, TBI, and significant cardiorespiratory compromise (e.g. COPD). However, present substance abuse of nicotine products will be permitted. All participants with contraindication to obtaining MRI scanning or those with claustrophobia will be excluded.

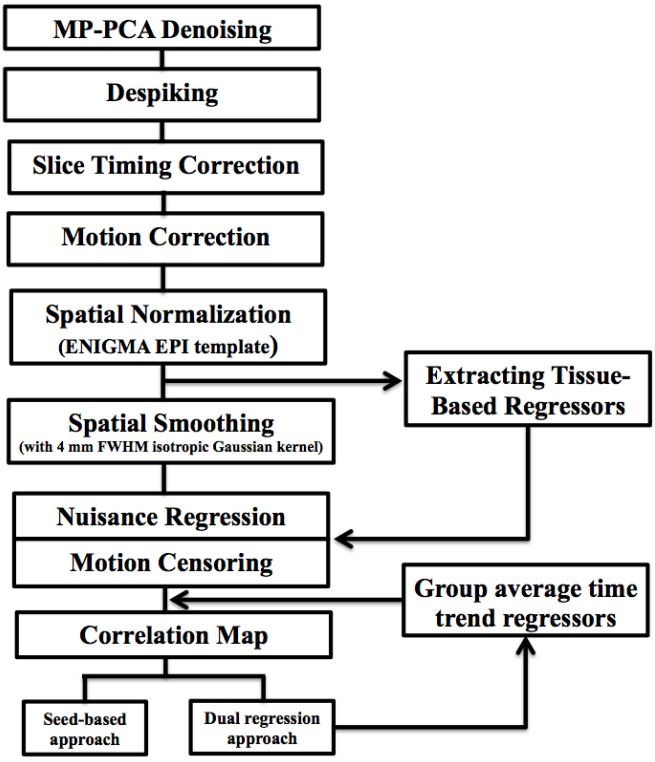

Figure 1. Flowchart of ENIGMA rsfMRI analysis pipeline (adapted from Adhikari *et al* (2018)).

Preprocessing: Following the ENIGMA analysis pipeline for resting-state fMRI data implemented in the AFNI software (Fig. 1) (Adhikari *et al*, 2018), we will first apply Marchenko-Pastur distribution-based principal components analysis (MP-PCA) for denoising (Veraart *et al*, 2016), to improve signal-to noise ratio (SNR) and temporal SNR (tSNR) properties of the time series data, with no loss of spatial resolution of the image and without the introduction of additional partial volume effects. We will then correct spatial distortions associated with long-TE gradient echo imaging using the gradient-echo 'fieldmap' or the reversed-gradient approach. After that, we will correct the time of acquisition of each slice. Next, we will correct head motion by registering each functional volume to the volume with the minimum outlier fraction, where each transformation is concatenated with the transformation to standard space, to avoid unnecessary interpolation. We will further spatially normalize images to the ENIGMA EPI template in Montreal Neurological Institute (MNI) standard space for group analysis, and then smooth the images with a 4-mm kernel. We will then regress out the effects of nuisance variables such as the linear trend, 6 motion parameters (3 rotational and 3 translational directions), their 6 temporal derivatives (rate of change in rotational and translational motion) and time courses from the local white matter and cerebrospinal fluid (CSF) from lateral ventricles. Finally, we will censor the time points with excessive motion (> 0.2 mm) estimated as the magnitude of displacement from one time point to the next, including neighboring time points and outlier voxels fraction (>0.1) were censored from statistical analysis. We will make outlier

images based on the time points with excessive motion, and enter then into the individual-level general linear model to remove the influence of these time points on estimates of functional connectivity while maintaining the temporal structure of the data.

Individual-level Analyses: Voxel-wise seed-based functional connectivity analyses will be performed using the CONN toolbox (Whitfield-Gabrieli *et al*, 2012) and in-house scripts written in Matlab (version R2016b). The seed regions of interest will be amygdala, hippocampus, ACC and mPFC that are defined by the anatomical mask images from the WFU_PickAtlas software (http://fmri.wfubmc.edu/software/pickatlas).Following Kaiser *et al* (2016), the time course will be segmented into 36-s windows, sliding the onset of each window by 18 s, for a total of 15–19 windows (depending on length of the functional scan). The duration of sliding windows is selected to optimize the balance between capturing rapidly shifting dynamic relationships (with shorter windows) and achieving reliable estimates of the correlated activity between regions (Leonardi and Van De Ville, 2015). Next, the Fisher's z-transformed Pearson's correlation coefficient will be computed for each sliding window between the truncated time course of the seed and that of all other voxels, yielding a set of sliding-window beta maps for each participant. Dynamic rsFC will be estimated by calculating the SD in beta values at each voxel.

Group-level analyses: For each seed area, individual dynamic rsFC maps will be entered into a whole-brain t-test to investigate the between-group differences. Correlation analyses to examine the relationship between severity of PTSD and dynamic rsFC will be conducted within the PTSD group based on a correlation between CAPS scores and dynamic rsFC at each voxel per seed region. Age, sex, depression severity, traumatic brain injury (TBI), alcohol use, childhood trauma exposure, adult trauma exposure, medication status and scanner site will be included as covariates of no interest. Group-level effects will be considered significant if results are height-thresholded at $p < 0.001$ and survive $p < 0.05$ cluster-level false discovery rate (FDR) corrections. In the aforementioned mega-analysis, we will pool all subjects together to calculate the functional connections between seed areas and the rest of the brain, and will find some target areas significantly connected with seeds. The mega-analysis will include a covariate for site. Sites with multiple scanners will be subdivided into multiple sites. To avoid being biased by the mega-analysis due stratification or interaction effects, we will then extract the values of functional connections between seeds and targets, and enter them into a meta-regression approach to validate the findings. We will also explore available whole brain meta-regression analytic strategies.

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