ENIGMA PTSD Work Group Proposal: Structural Covariance Between Regions with Cortical Thickness Reduction in PTSD

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Introduction

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 [1]. Trauma and chronic stress elicit synaptic dysconnectivity [2,3] and synaptic density reduction [4] that are associated with brain morphometric changes. PTSD is accompanied with cortical thickness reduction in various brain regions [5,6] (however, see Li et al.[7]).

Structural covariance measures of cortico-to-cortical connectivity corresponding to transcriptional brain networks [8] and anatomical connectivity based on white matter fiber tractography [9]. It may index mutually trophic factors between distant regions that are anatomically connected. Structural covariance is sensitive to aberrant connectivity and brain network organization in PTSD [10-12]. It is speculated that neural connections can propagate pathological processes to distant cortical regions [13].

A study recently published in American Journal of Psychiatry [13] reported that Structural covariance was significantly increased among regions with the most extensive thickness reductions, irrespective of whether it was measured in patients or healthy control subjects. The findings suggest that cortico-cortical connectivity can provide an explanation for the irregular topographic distribution of thickness reduction, and the regions that are affected in patients are part of networks that are present in healthy individuals.

Little is known about the association between cortical thickness reduction and structural covariance in PTSD. Few studies have reported structural covariance between all pairs of regions in PTSD, which may be due to the difficulty of detecting significance after correcting multiple comparisons. Moreover, studies of PTSD based on small samples are hard to fully understand the effects of variables such as age, gender, trauma experience, and are hard to reveal robust and generalizable results. We aimed to investigate the structural covariance between regions with cortical thickness reduction in PTSD. We specifically hypothesized that the structural covariance between regions with cortical thickness reduction in PTSD patients would be stronger compared with the structural covariance between randomly selected regions in both PTSD and controls, would be stronger in patients with PTSD than in controls, would be stronger in PTSD patients with more severe symptoms, and would be modulated by factors such as age and gender.

Methods

Participants

The ENIMGA-PGC PTSD Working Group aggregated data from 29 cohorts in five countries. PTSD patients and control subjects had varying levels of trauma exposure. We will analyze cortical thickness data from 3,505 subjects, including 1,344 PTSD patients and 2,131 control subjects. Harmonized scales of childhood trauma and alcohol use disorder (AUD) were obtained from the sites in addition to SCID diagnoses and PTSD severity scale scores. All participating sites obtained approval from local institutional review boards and ethics committees. All study participants provided written informed consent.

Imaging and Statistical Analysis

Raw structural imaging (T1) data obtained from previously conducted cross-sectional case-control studies were analyzed at Duke University through a standardized neuroimaging and QC pipeline developed by the ENIGMA Consortium (need citation). Cortical parcellation was performed with FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) that calculates regional mean cortical thickness and surface area measures for 148 regions (74 outputs in each hemisphere according to the Destrieux Atlas [14].

Structural Covariance Analysis

The pipeline of the structural covariance analysis is shown in Fig. 1. The influence of age, sex, and study site were regressed out from the association with cortical thickness values. Age was not regressed out when investigating the interaction of diagnosis and age, and sex was not regressed out when investigating the interaction of diagnosis and sex. After this step, group-specific matrices of structural covariance between all possible pairs of 148 were calculated based on Pearson's correlation coefficients. The r-to-z transformation was applied to all correlation coefficients to improve normality [13]. Cortical regions were ranked from highest to lowest according to the effect size of cortical thickness reductions.

To investigate whether structural covariance is significantly stronger between regions with cortical thickness reductions compared with randomly selected sets of regions, we will employ permutation testing for structural covariance measured in each subject group separately and for the between-group difference. The mean structural covariance between the top-*n* regions with the most significant cortical thickness reductions will be computed. To generate a null distribution for this mean value, the mean structural covariance will be computed between 5,000 randomly chosen sets of *n* regions. The proportion of random region sets for which the mean structural covariance exceeds or equals the mean structural covariance in the actual (nonrandom) data will provide a p value for the null hypothesis of equality in structural covariance among regions of cortical thickness reductions and randomly chosen pairs of regions. This procedure will be repeated independently for n=2,…,148, and the mean structural covariance between the top-*n* regions with the most significant cortical thickness reductions will be plotted as a function of *n*. The area under this plot of mean structural covariance as a function of *n* will be used to compute a global p value for all values of *n*.

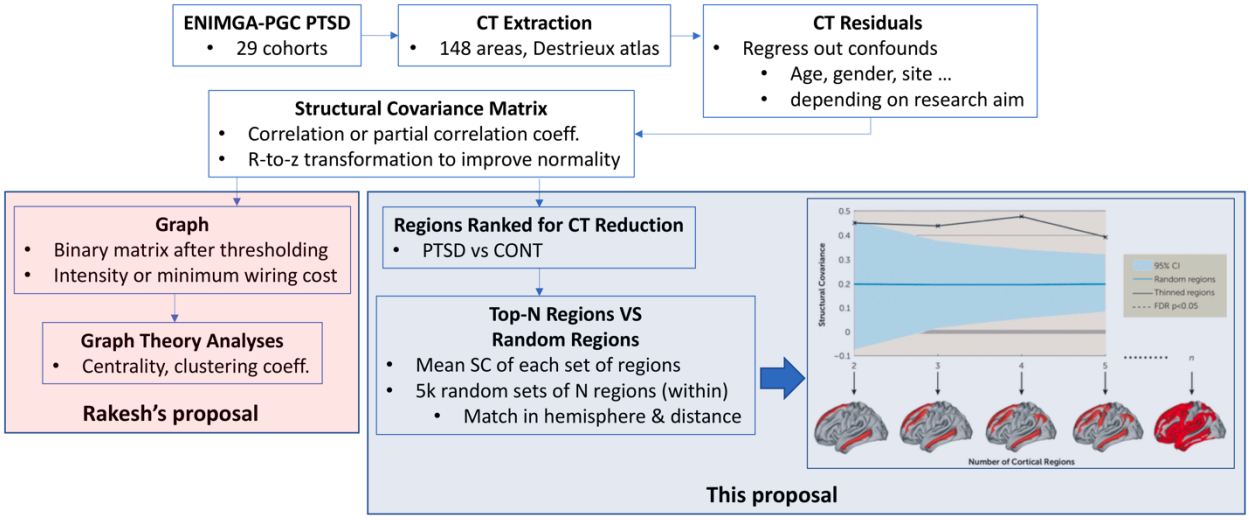

Figure 1. Pipeline for structural covariance analysis.

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