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.

Post-traumatic stress disorder (PTSD) is an illness that has a lifetime prevalence of 6.8% among adult Americans (1). PTSD is present in 4-10 % of OEF/OIF veterans (2) and poses significant burden to society and the health system (2, 3). The neuroscience of PTSD includes abnormalities in fear conditioning (negative reinforcement), dysregulation of brain circuits (vmPFC-amygdala circuit), memory reconsolidation abnormalities and epigenetic interactions with instances of trauma (4). Short term and longitudinal studies have shown changes in brain structure as a result of PTSD (5). In addition to structural changes (5) (reduction in volumes of hippocampus and amygdala; grey matter cortical thinning in DLPFC, OFC, insula, ACC), studies have shown changes in functional activity in specific brain regions (hyperactivity in amygdala, hypoactivity in vmPFC, hippocampal activity disruption, insular hyperactivation) (6, 7).

Some common methods used to study brain networks in PTSD include:- 1) electrophysiological networks derived from EEG or MEG data 2)functional connectivity activations from resting state or task related fMRI (8, 9)3) structural connectivity networks derived from DTI data (10) 4) structural connectivity networks delineated by between subject intraregional correlations in measures of cortical thickness or gray matter volume (otherwise called structural covariance network analyses) (11-13).

Applying graph theory to brain imaging has helped to assess structural and functional connectivity between different regions (14). Graph theory describes a network as a system of nodes and edges. Nodes typically represent brain regions for which the property of interest is known and the edges represent the strength of the correlation between any two regions based on the similarity of this property. The result is a correlation matrix that describes this relationship for every possible combination of regions (14).

Structural covariance network analyses is a network connectivity based application of graph theory to brain imaging (11, 15). Cortical morphometric network analysis can be used to check for correlations between brain regions across individuals. It is hypothesized that these structural connectivity networks based on between subject intraregional correlations in cortical thickness measures may represent functional association, or possibly unique information on interactions between brain networks. Unlike functional MRI, structural covariance network analyses is less likely to be affected by task requirements or subjects' responses during scanning. Positive correlations between cortical thicknesses have shown to correlate to structural diffusion connections, unlike negative correlations (15).

Four centrality measures (degree, closeness, betweenness, eigen vector) are tangible outcome measures from structural covariance analyses using cortical thickness and subcortical grey matter volumes (5). One centrality measure (nodal betweenness centrality) is defined as fraction of all shortest paths that pass through an individual node. Path length is minimum number of unique edges connecting 2 nodes. Betweenness centrality indicates the importance of a node in a

network. The centrality measures are degree centrality (number of directly interconnected nodes), betweenness centrality (frequency with which a node falls between pairs of other nodes on their shortest interconnecting path), closeness centrality (normalized number of steps required to access every other node from a given node in a network, adapted from the distance function in the Brain Connectivity Toolbox), and eigenvector centrality (a spectral centrality measure based on the idea that the importance of a node is related to the importance of the nodes connected with it) (11, 14).

Three previous studies have used structural covariance analyses to show centrality differences between children, adolescent and adults with and without PTSD (12, 13, 16). These studies measured centrality differences between healthy controls, maltreated children (age 9-10 years) who developed PTSD versus those who did not (12); centrality measures in veterans with active versus remitted PTSD (16); as well as differences between adolescents (mean age 14-15 years) with no trauma history, compared to maltreated adolescents who developed versus did not develop PTSD (13). Compared to healthy controls, subjects with either a lifetime history of PTSD or current PTSD showed greater centrality in right superior frontal sulcus (16). The study also showed centrality in right subcallosal gyrus, left frontal pole, and right superior frontal sulcus to be associated with remission of PTSD symptoms (16).

In the second study, which looked at children (Mean age of 10 years), maltreated children with PTSD had greater centrality in the right PCC and lower centrality in left ACC. Low centrality in right IFC was associated with H/O maltreatment. Resilience to PTSD following maltreatment was associated with centrality differences in the right FP (transverse frontopolar gyri and sulci) and the left ACC. Maltreated youth without PTSD exhibited larger centrality in this area than the other two groups (12).

The third study looked at adolescents (mean age range of 14-15 years) and showed that maltreated youth with PTSD had larger centrality than both maltreated youth without PTSD and controls in the left ACC and smaller centrality in the right OFC than maltreated youth without PTSD. They also showed larger centrality than controls in the right insula/inferior frontal cortex. In addition, maltreated youth with and without PTSD compared to non-maltreated controls showed smaller centrality in the right temporal pole (13). This study's results contrasted to the study in younger children, especially with regard to the role of left ACC which could be attributed to the effect of growth and development on neurobiology of PTSD, differences in scanner characteristics and not including sub-cortical regions in analyses (13).

These 3 studies were done with small sample sizes (300s in the first study and 100s in the second study). None of them have used sub-cortical volumes in analyses.

We propose to apply the structural covariance network analyses to obtain centrality measures using subjects from PGC-PTSD neuroimaging dataset. One study has looked at this analysis in PTSD subjects using DTI measures and this included sub-cortical volumes (10). Hitherto only one study has looked at structural covariance analyses combining cortical thicknesses and sub cortical volumes (5). A few studies have looked at structural covariance network analyses with sub-cortical

structures (combining cortical thicknesses and subcortical volumes) in conditions apart from PTSD (17-19).

B. Analyses Plan

Using data from the PTSD Psychiatric Genetics Consortium (PGC-PTSD) neuroimaging project, we will extract cortical thicknesses of 148 brain regions based on Destrieux Halgren parcellation atlas (20). We have 2 groups of subjects – trauma exposed controls and subjects with PTSD currently. Both these groups would have subjects with and without childhood trauma. Sub-cortical volumes available include thalamus, caudate, putamen, hippocampus, amygdala, nucleus accumbens and pallidum (14 regions across both hemispheres). These volumes will be analyzed separate from cortical thicknesses. We will also perform structural covariance comprising 12 hippocampal subfields in both these groups of subjects. The PGC-PTSD dataset consists mostly of veterans and some children and adolescents. Possible covariates for the data include age, gender, and childhood trauma score, alcohol use/use of other substances, comorbid MDD /other comorbid disorders, and age of index trauma.

In separate analyses, we will use cortical thicknesses and sub-cortical grey matter volumes. We will regress out the influence of other cortical areas using covariates (which is possible due to large sample sizes). We will proceed with analyses in the following fashion – 1) generate interregional partial correlation matrices for each group by calculating partial correlation coefficient for all regional pairings of cortical thickness/grey matter volume measures across subjects in each group, 2) calculate minimum wiring cost and corresponding thresholds for each group, 3) calculate centrality measures (degree, closeness, betweenness, and eigen vector) use the functions in the Brain Connectivity Toolbox to, 4) test the reliability of centrality measures through Jackknife resampling methods and 5) perform pairwise group comparisons of centrality based on permutation testing with 10,000 iteration that shuffles the group classification. The planned pairwise group comparisons are (1) current PTSD with childhood trauma versus current PTSD without childhood trauma (2) Trauma exposed controls with childhood trauma versus trauma exposed controls without childhood trauma (3) current PTSD with childhood trauma vs trauma-exposed controls with childhood trauma (4) Current PTSD without childhood trauma (Least resilient) versus trauma exposed controls with childhood trauma (Most resilient).

Hypotheses for adults in the age group 20-50

Primary hypotheses (Atlas area numbers next to names of regions)

Current PTSD

1. Larger centrality in right PCC (9), right insula (17,18), left insula (Inferior segment of the circular sulcus of the insula – 48), right precuneus (30), right orbital part of IFG (13) and right inferior frontal gyrus (12, 14) in current PTSD compared to trauma exposed controls.
2. Lower centrality in left frontal pole (5), left OFC (13), right temporal pole (34,35,36) and left ACC (7) in current PTSD compared to trauma exposed controls.
3. Decreased centrality in bilateral hippocampus, amygdala, and thalamus (when all cortical thicknesses and subcortical volumes are combined)

Trauma exposed controls

4. Trauma exposed controls have higher centrality in right FP (5) (transverse frontopolar gyri and sulci and left ACC (6) (Markers of resilience), and lower centrality in right superior frontal sulcus (54) compared to both other groups.
5. Higher centrality in right orbital part of IFG (13), triangular part of right inferior frontal gyrus (14).

Childhood trauma

Centrality differences in hippocampal subfields and amygdala volumes in subjects with childhood trauma (current PTSD and and trauma exposed controls) compared to subject without childhood trauma (current PTSD and and trauma exposed controls).

Number of subjects in the dataset: -

Cortical thicknesses – 3023 (includes subjects with PTSD and healthy controls)
Subcortical volumes - 3186 (includes subjects with PTSD and healthy controls)
Hippocampal subfields - 3500 subjects (includes subjects with PTSD and healthy controls)

C. Analyses Personnel

1. Gopalkumar Rakesh
2. Delin Sun
3. Emily Clarke
4. Rajendra Morey
5. Xin Wang
6. ENIGMA-PTSD Workgroup
7. PGC-PTSD Neuroimaging Workgroup

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.
1. Extracted subject cortical thicknesses, subcortical volumes and hippocampal subfields from PGC-PTSD dataset.
2. Data on covariates - age, gender, childhood trauma score, alcohol use/use of other substances, comorbid MDD/other comorbid disorders, and age of index trauma.

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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