PGC Secondary Analysis Proposal *(v2, revised 02-2015, pfs)*

Date	July 26, 2018
Title	The shared and unique effects of childhood adversity on subcortical volumes, hippocampal subfields, cortical thickness, and surface area in MDD and PTSD.

Investigative Team. Underline PGC PI taking responsibility for all aspects of this proposal.

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Data access requested. No permission required for published results (only pre-publication)

Group	Individual genotypes	Summary results	Permission from group?	Version (e.g., MDD2, SCZ3)
ADHD				
AN				
AUT				
BIP				
Drug/alcohol				
MDD				
OCD/TS				
PTSD				
SCZ				

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.

Although the literature is replete with studies linking childhood trauma to clinical conditions such as MDD and PTSD, the unique and shared structural brain signatures across these conditions in the context of childhood adversity remains unknown. The current proposal will address this critical gap in the literature (Aim 1), will examine potential sex differences in associations between childhood adversity and brain structure (Aim 2), and will explore how specific types of childhood trauma influences brain structure in MDD and PTSD (Exploratory Aim 3).

B. Analytic Plan

Provide a brief description of the analyses to be performed to address the research questions described above. Include relevant details e.g. phenotype definition, QC, analysis, plans to address population stratification and other confounders, power.

The project is a mega-analysis that requires FreeSurfer-derived individual measures for subcortical volume (7 bilateral regions: amygdala, caudate, hippocampus, nucleus accumbens, pallidum, putamen, thalamus), 12 hippocampal subfields, cortical thickness and surface area (148 regions based off of the Destriuex atlas), and covariates (e.g., ICV, site, age, sex), as well as individual-level total scores and subscores from the Childhood Trauma Questionnaire (CTQ). For our primary analyses (Aims 1-2), we will use generalized estimating equation (GEE) models implemenented in R to estimate the linear effects of CTQ scores (dimensional measurement), diagnosis (grouping variable with 3 levels), sex (grouping variable with 2 levels), and any relevant covariates while accounting for the fact that the outcome variables (i.e., brain regions) are correlated. For our exploratory analyses (Aim 3), we will use established cutoff scores of CTQ subscales to examine potential differential effects of neglect and abuse (modeled as grouping variables with 3 levels of severity of exposures). For all analyses, final inclusion of covariates will be determined by model fitting. We may also run subanalayses with and without non-civilian samples, given the uniqueness of combat experience.

Thus far, we have identified 14 sites from ENIGMA-MDD that have both CTQ and MRI data (total N=3872) and 12 sites from ENIGMA-PTSD that have both CTQ and MRI data (total N=1311).

C. Analytic Personnel

Indicate who will be responsible for performing the analyses.

Tiffany Ho, Lauren Salminen, Mark Logue

D. Resources Needed

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

The data are already collected (although there is new MDD data from Stanford that needs QCing) and only certain variables (e.g., depression scores from PTSD) would be needed from a subset of sites. Resources will involve existing computational server time, ENIGMA protocols, and access to existing scripts. Research assistants at Stanford will be involved with organization, coding, and optimzation.

F. Timeline

Estimate time required to complete the plan and write a paper (should be ≤ 6 months).

The data are already collected and with the exception of the item-level symptom measurements should be available immediately. The dsicussion of appropriate statistical models and first data analyses should occur by December 2018 and final data analyses should be done by March 2019. Manuscript will be sent for circulation April 2019 and submitted for publication June 2019.

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

This is an extremely important part of this proposal. Describe how authorship will be handled in the manuscript resulting from this analysis. To avoid a revision, first review the authorship policy of the group(s) whose data you wish to analyze. Points to consider:

(a) are you following the authorship policies of the groups involved?

(b) will there be a writing group and if so, who will be included?

(c) what groups or individuals will be listed as authors?

(d) will PGC members not listed as named authors be listed at the end of the manuscript?

(e) will PGC members or groups be listed as "collaborators" on the PubMed abstract page?

(f) how will funding sources be handled or acknowledged?

Authorship credit will be based on (1) contributing or generating structural MRI data to the proposed analyses; (2) contributing to the conception, design, analysis, and/or interpretation of the data; (3) drafting the manuscript or revising it critically for important intellectual content; (5) final approval of the manuscript to be published. People involved in the primary design, analysis, and writing parts of the project will be listed as (or joint-first, denoted with an asterisk) and senior (last or joint-last). In addition, the ENIGMA MDD and PTSD Working Group chairs and all sites who contribute data will be listed as co-authors.