ENIGMA-PGC PTSD Proposal

A Comparison of Methods to Harmonize Cross-Platform Neuroimaging Data

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Methods for Harmonization of Neuroimaging Data

The ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis; http://enigma.ini.usc.edu) Consortium is a large international cooperation project that aggregates neuroimaging, demographic, and clinical data in participants from multiple sites, aiming at increasing statistical power and leading to findings that are more representative of the general population (Dennis et al., 2020; Thompson et al., 2014). Neuroimaging studies based on the ENIGMA cohorts may be more robust and more representative of the population with PTSD given that the same preprocessing protocol was applied in all sites participating in an ENIGMA project. However, the results may still be biased by site-related differences in participants' demographic and clinical information, acquisition protocols, and scanning platforms (Radua et al., 2020). Different approaches have been developed to harmonize neuroimaging data across sites. The linear mixed-effects (LME) model considers study site as a random factor and produces results with higher statistical power than the widely used random-effects meta-analysis approach (Boedhoe et al., 2017; Favre et al., 2019; van Rooij et al., 2018). The ComBat approach was developed to remove the site differences while preserving variations due to biologically relevant covariates such as age, sex, and diagnosis (Fortin et al., 2018). ComBat overcomes the limitations of the LME method by assuming varying normal distributions at different sites. ComBat has been successfully used in recently published studies to harmonize neuroimaging data including cortical thickness (Fortin et al., 2018), surface area and subcortical volume (Radua et al., 2020), diffusion tensor imaging (Fortin et al., 2017), and resting-state functional connectivity (Yu et al., 2018). The newly published method by Pomponio et al. (2020) further improves the ComBat approach by allowing for non-linear trend in the data using Generalized Additive Models (GAMs; we thus call this approach ComBat-GAM) and assuming different distributions for the multiplicative (scale, or variance) and additive (location, or mean) effects, respectively. The ComBat-GAM method outperformed the traditional ComBat approach

in harmonizing cortical and subcortical grey matter volumes in a large sample of 10,477 healthy subjects (3-96 years old) aggregated from 18 sites (Pomponio et al., 2020).

Test Case for Comparing Methods

We select cortical thickness data in trauma-exposed people with and without PTSD to compare cross platform harmonization. PTSD is associated with anatomical and functional alternations in widely distributed regions that play a role in fear learning, threat detection, executive function and emotion regulation, and contextual processing (Shalev, Liberzon, & Marmar, 2017). These include inferior temporal regions (Clausen et al., 2020), default model network (DMN), salience network (SN), central executive network (CEN) and the others (Sripada et al., 2012; Yehuda et al., 2015; Zandvakili et al., 2020). Inconsistent results in PTSD concerning cortical thickness point to an increase (Li et al., 2016), decrease (Lindemer, Salat, Leritz, McGlinchey, & Milberg, 2013; Wrocklage et al., 2017), and even no significant change (Rinne-Albers et al., 2020). Furthermore, little is known about the age-related trajectories of cortical thickness in PTSD, whereas age-appropriate cortical thickness decline is typical in human brain development (Frangou et al., 2020). Military service members with traumatic brain injury and PTSD have faster declines in cortical thickness (Santhanam, Wilson, Oakes, & Weaver, 2019; Savjani, Taylor, Acion, Wilde, & Jorge, 2017) and surface area (Santhanam, Wilson, Mulatya, Oakes, & Weaver, 2019). PTSD-related changes in cortical thickness may be associated with faster chronological age (Katrinli et al., 2020) and DNA methylation age (Wolf, Logue, et al., 2016) (however, see Connolly et al. (2018)). It is possible that PTSD may enhance the association between cortical thickness reduction and metabolic syndrome including cardiometabolic pathology, neurodegeneration, premature aging, and therefore leads to significant medical and cognitive decline (Wolf, Sadeh, et al., 2016).

A. Research Aims and Hypotheses

Aims. In the present study, we aim to compare results from three different harmonization approaches (1) LME, (2) ComBat, and (3) ComBat-GAM. We propose comparing methods using cortical thickness data from 29 ENIGMA-PTSD sites as a test case to investigate age-related trajectories of cortical thickness in participants with PTSD.

Hypotheses. We hypothesize more statistically significant between-group differences in age-related cortical thinning through utilization of ComBat-GAM relative to LME and ComBat.

B. Analyses plan

Participants. All data were aggregated by the PGC-ENIGMA PTSD Working Group from 29 sites located in five countries (PTSD/Non-PTSD N = 1,344/2,073). Most sites used clinician-administered measures such as the Structured Clinical Interview (SCID) (First, 2015) or Clinician-Administered PTSD Scale (CAPS) (F. W. Weathers et al., 2018; F. W. Weathers, Keane, & Davidson, 2001) to ascertain PTSD diagnosis. One site used a psychiatrist diagnosis for PTSD, and a few additional sites used self-report scales such as the PTSD Checklist (PCL) (F.W. Weathers et al., 2013). While the majority used DSM-IV criteria, a small subset of sites used DSM-5 criteria. Severity of PTSD symptoms was derived from the same measures used for diagnosis, except when a clinician-administered measure (e.g., SCID) lacked severity information, the PCL or Davidson Trauma Scale (DTS) (Davidson et al., 1997) was used. The measures reflect PTSD diagnosis and symptoms in the past month before scanning. For depression, sites used a mix of clinician-administered and self-report instruments to diagnose depression. We will harmonize depression data by assigning participants to major depressive disorder (MDD) or control groups based on a standardized depression severity cut-off. The majority of sites reported depression severity using the Beck Depression Inventory-II (BDI-II) (Beck, Steer, & Brown, 1996), while other commonly used scales were the Center for

Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), Depression Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995), and Children's Depression Inventory (CDI) (Kovacs, 1985). All study sites obtained approval from local institutional review boards or ethics committees. All participants provided written informed consent.

Imaging Data Preprocessing. Anatomical brain images were preprocessed at Duke University through a standardized neuroimaging and QC pipeline developed by the ENIGMA Consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols/) (Logue et al., 2018). Cortical thickness measurements were generated by FreeSurfer software (https://surfer.nmr.mgh.harvard.edu) based on the Destrieux atlas (Destrieux, Fischl, Dale, & Halgren, 2010) that contains 74 regions per hemisphere. In brief, white matter surfaces were deformed toward the gray matter boundary at each surface vertex. Cortical thickness was calculated based on the average distance between the parcellated portions of white and pial surfaces within each region. The estimates of cortical thickness for each region and participant were entered into further respective analyses. The image quality was estimated by the Euler number, which is a measure of the topological complexity of the reconstructed cortical surface (Dale, Fischl, & Sereno, 1999).

ComBat Harmonization. The ComBat approach removes the effects of study sites and/or scanners while preserving inherent biological associations in the data (Fortin et al., 2018). It achieves harmonization by first modeling expected imaging features as linear combinations of the biological variables and site effects whose error term is further modulated by site-specific scaling factors. After that, it applies empirical Bayes to improve the estimation of site parameters for small samples. In the present study, PTSD diagnosis, age, and sex will be designated as biological variables. The ComBat approach will be implemented using the R scripts (https://github.com/Jfortin1/ComBatHarmonization) running on RStudio (ver. 1.3.1073) and R (ver. 4.0.2).

ComBat-GAM Harmonization. Compared to the traditional ComBat approach, the ComBat-GAM method specifies covariates with generic nonlinear effects using the generalized additive models (GAM) (Pomponio et al., 2020). In the present study, we specify age as a nonlinear term in the model for our research purpose. The ComBat-GAM approach will be implemented using the Python scripts (https://github.com/rpomponio/neuroHarmonize) running on Anaconda (ver. 4.8.2) and Python (ver. 3.7.6).

Statistical Models. For the tests based on the LME model, the estimates of cortical thickness from all the participants will be entered into a linear mixed-effects model per cortical region with study site as a random factor, and age, sex, PTSD diagnosis, and age by PTSD diagnosis interaction as covariates. For the analyses based on ComBat and ComBat-GAM approaches, the estimates of cortical thickness from all the participants will be first harmonized through the ComBat or ComBat-GAM approach, and then entered a linear model per cortical region with age, sex, PTSD diagnosis and age by PTSD diagnosis interaction as covariates. The covariate of depression diagnosis will also be added to test the robustness of the findings. The PTSD symptom severity will be utilized to replace PTSD diagnosis in the models to investigate the associations between PTSD severity and age. The false discovery rate (FDR) method (Benjamini & Hochberg, 1995) with a *q*-value threshold of 5% will be employed to correct for multiple comparisons across the 148 cortical regions. The R packages *lme4, lmerTest* and *sjPlot* will be utilized for statistical analyses.

C. Analyses Personnel

Delin Sun, PhD

D. Resources Needed

1. Preprocessed cortical thickness data by the ENIGMA-PGC PTSD Consortium.

2. Demographic information including age, sex and sites/scanners, and clinical variables including PTSD diagnosis, symptom severity, and comorbid depression.

E. Timeline

First results report is anticipated within two months.

F. Collaboration

Follow the standard PGC policy regarding secondary analyses, ENIGMA-PGC investigators who wish to substantively contribute to this project are welcome to discuss with and join the proposing group.

G. Authorship

We will follow the authorship policy of the PGC-PTSD (https://pgc-ptsd.com/wpcontent/uploads/2017/06/Authorship-Guidelines-PGC-PTSD.pdf)

a) Are you following the authorship policies of the groups involved? **YES**

b) Will there be a writing group and if so, who will be included? **Delin Sun, Rajendra A. Morey, Joaquim Radua, and Aris Sotiras will be included in the writing group.**

c) What groups or individuals will be listed as authors? **Authors will include the writing group and individuals and group contributors of data and analysis from each site (generally 2-5 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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