# *PGC Secondary Analysis Proposal* *(v2.1, revised 05-2015)*

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| **Date** | ***7/13/2018*** |
| **Title** | ***Epigenomic Predictors of Brain Aging in PTSD*** |

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

| Name | Email | PGC group |
|---|---|---|
| ***Anthony S. Zannas*** | ***aszannas@gmail.com*** | |
| ***Rajendra Morey*** | ***rajendra.morey@duke.edu*** | |
| ***Monica Uddin*** | ***muddin@illinois.edu*** | |
| ***Alicia Smith*** | ***Alicia.Smith@emory.edu*** | |
| ***Erika Wolf*** | ***Erika.Wolf@va.gov*** | |
| ***Caroline Nievergelt*** | ***cnievergelt@ucsd.edu*** | |

***Specific data access requested. Individual genotypes always require permissions. For summary results, no permission required for anything posted on PGC downloads. Permissions needed for all other summary result files (e.g., pre-publication, individual studies, M vs F, etc.)***

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

Several lines of evidence suggest that PTSD is associated with accelerated brain aging. Individuals with PTSD exhibit molecular markers of cellular aging, reductions in the volume of age-susceptible brain regions, and faster age-related cognitive decline. Epigenetic modifications play central role in neural processes and aging-related phenotypes, but their tissue-specific nature impedes discovery of their potential role in PTSD-related brain aging. It is thus necessary to assess epigenetic signatures that may be conserved across tissues using easily accessible biological material, such as blood or saliva. To address these questions, the goal of the proposed project will be to identify peripheral epigenomic predictors of brain aging from cross-sectional data in PTSD. This goal will be pursued along two aims: 1) identify composite DNA methylation-based markers and/or distinct DNA methylation sites in either blood or saliva that may be associated with accelerated structural MRI-predicted brain aging and/or its rate of change; and 2) test whether PTSD/control case status and/or other parameters (such as sex, lifestyle factors, and blood cell composition) moderate these associations.

### *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.*

Brain age can be estimated from available structural MRI data at each site using a recently established method and publicly available software (https://github.com/BIDSApps/BARACUS). The difference between MRI-predicted brain age and chronological age is proposed as a measure of accelerated brain aging and represents the primary study endpoint. Regression models will include as dependent variables both the baseline accelerated brain aging (cross-sectional analysis) and, if available, the intra-individual change in brain aging over time.

Epigenetic analyses will be conducted using baseline DNA methylation array (450K or EPIC) data available at each site. As composite epigenetic markers, promise has been shown for DNA methylation-based predictors of age that estimate chronological age from several tissues and methylation sites across the genome. The difference between DNA methylation-predicted (epigenetic age) and chronological age is proposed as a measure of accelerated biological aging associated with several aging-related neuropsychiatric phenotypes. DNA methylation-based age

prediction –using markers such as the Horvath and Hannum epigenetic clocks- has already been performed at some PGC-PTSD cohorts and will be conducted at any additional participating sites using established bioinformatics methods. Beyond such composite markers, the project will also explore whether accelerated brain aging is associated with DNA methylation levels at distinct epigenome sites, after correction for multiple comparisons.

### *C. Analytic Personnel*

*Indicate who will be responsible for performing the analyses.*

*Primary analyses have already been performed/will be performed by investigators with expertise in structural MRI and DNA methylation analysis at each participating site with harmonization oversight by Rajendra Morey.*

*Secondary analysis will be led by Anthony Zannas (expertise in epigenetic analyses) and Rajendra Morey (expertise in structural MRI analyses).*

*Support will be provided by Alicia Smith (expertise in DNA methylation/epigenetic aging), Monica Uddin (expertise in DNA methylation/mental illness), and Erika Wolf (expertise in epigenetic aging/PTSD).*

*Support for integration of epigenetic and imaging data will be provided by Caroline Nievergelt.*

### *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.*

*Primary (dependent/independent) variables: 1) MRI-predicted brain age; 2) DNA methylation-predicted age; and 3) DNA methylation levels at individual methylation sites.*

*Covariates: 1) chronological age; 2) sex; 3) DNA methylation-calculated cell type composition (e.g. Houseman); 4) PTSD case/control status; 5) more specific PTSD symptoms if available (intrusive symptoms, heightened arousal, avoidance, etc.); 6) genome-wide SNP-based principles components (to control for population stratification); and 7) information on smoking, alcohol, and other substance use.*

*Analytic support as described above.*

### *F. Timeline*

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

*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*

*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 address:*

*(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?*

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***
*(b) will there be a writing group and if so, who will be included?* ***The writing group will be comprised of the investigative team 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.***