

## **Supplementary Materials**

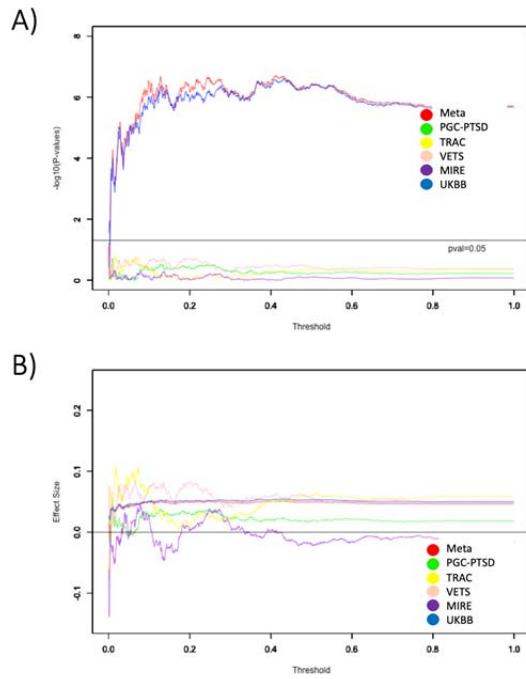
### **Supplementary Methods**

In addition to examining the dichotomous PTSD diagnosis variable, we examined a PTSD severity (PTSDsev) variable. For almost every cohort, this was assessed using the CAPS or PCL (see Supplementary Table 1 for details). The stage 2 and stage 3 models were very similar to those fit for PTSD. That is, in stage 2, linear models were fit with PTSDsev as the response, and the same set of predictors. A mixed model was used for VETSA to allow for correlation within twin pairs. In Stage 3, the main effect for PTSDsev and a PTSDsev x PGS interaction were added to the models of subcortical volume.

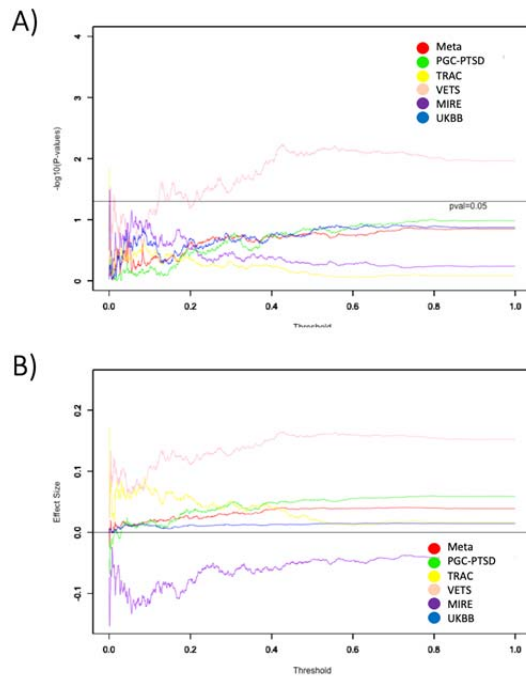
### **Supplementary Results.**

The Stage 2 PTSDsev analyses yielded similar results to the dichotomous PTSD analysis. That is, the PGS for hippocampal volume was not associated with PTSDsev. When examining other cortical regions, only the amygdala PGS was associated with PTSDsev (beta=-0.27, p=0.036), with significance similar to that observed with PTSD (OR=1.15, p=0.011). The stage 2, the interaction effect of PTSDsev and hippocampal volume PGS negative effect, as estimated for PTSD, but only at the trend level (p=0.084). For all other subcortical volumes, the interaction of PTSDsev and PGS was not significant (p>0.10).

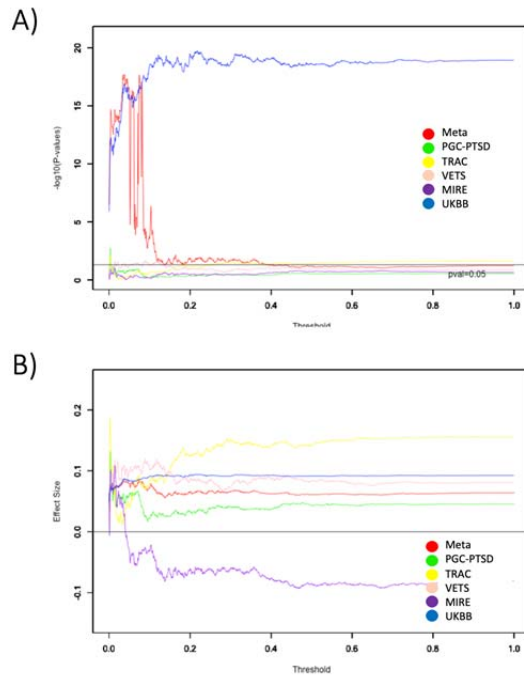
**Supplementary Figure 1:** Accumbens PGS: The significance (**A**) and effect size estimate (**B**) of the PGS predicting accumbens volume as a function of the threshold.



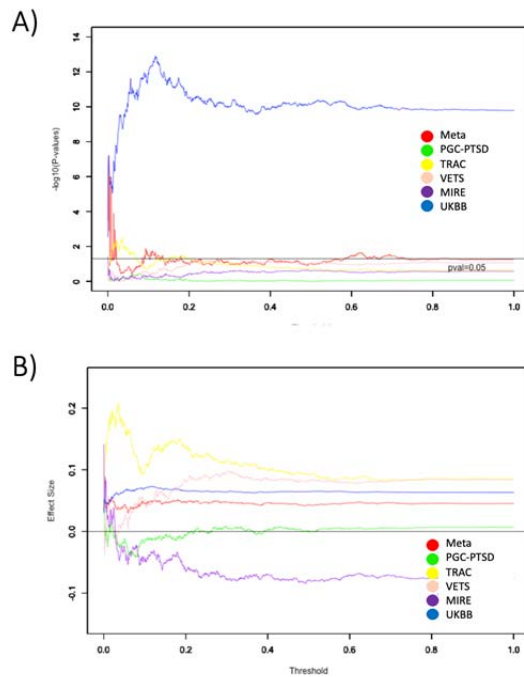
**Supplementary Figure 2:** Amygdala PGS: The significance (**A**) and effect size estimate (**B**) of the PGS predicting amygdala volume as a function of the threshold.



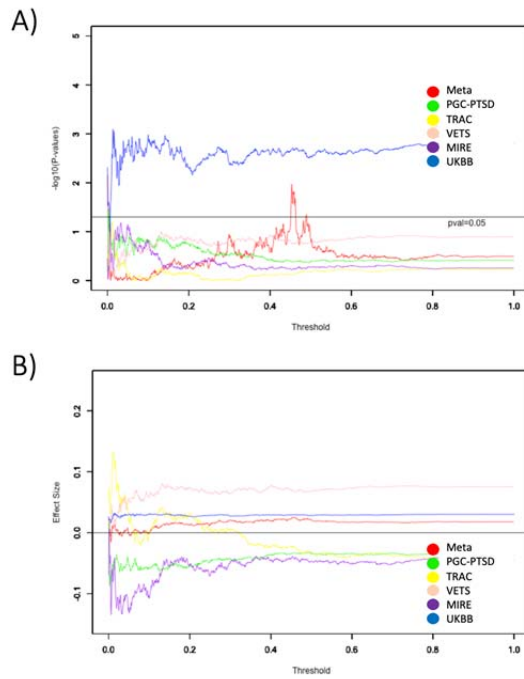
**Supplementary Figure 3:** Caudate PGS: The significance (A) and effect size estimate (B) of the PGS predicting caudate volume as a function of the threshold.



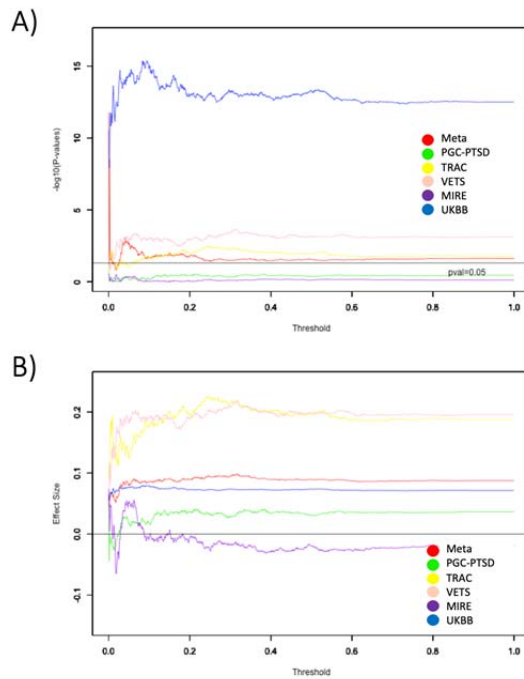
**Supplementary Figure 4 – Hibar et al. 2015 GWAS Hippocampal PGS:** The significance (A) and effect size estimate (B) of the PGS predicting hippocampal volume as a function of the threshold.



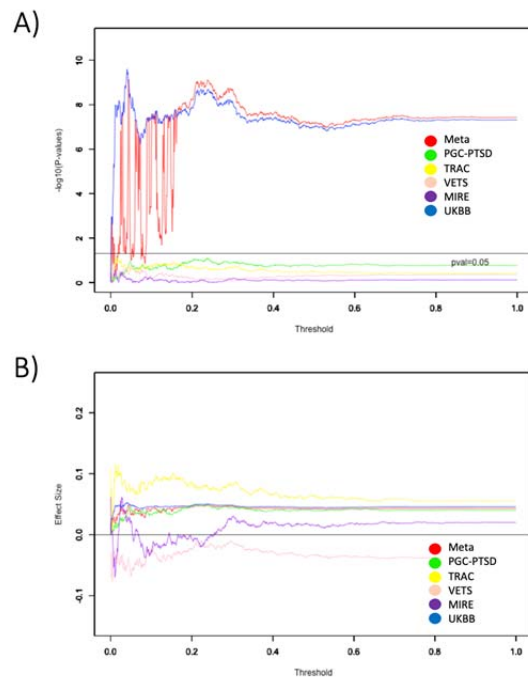
**Supplementary Figure 5** –Pallidum PGS: The significance (**A**) and effect size estimate (**B**) of the PGS predicting pallidum volume as a function of the threshold.



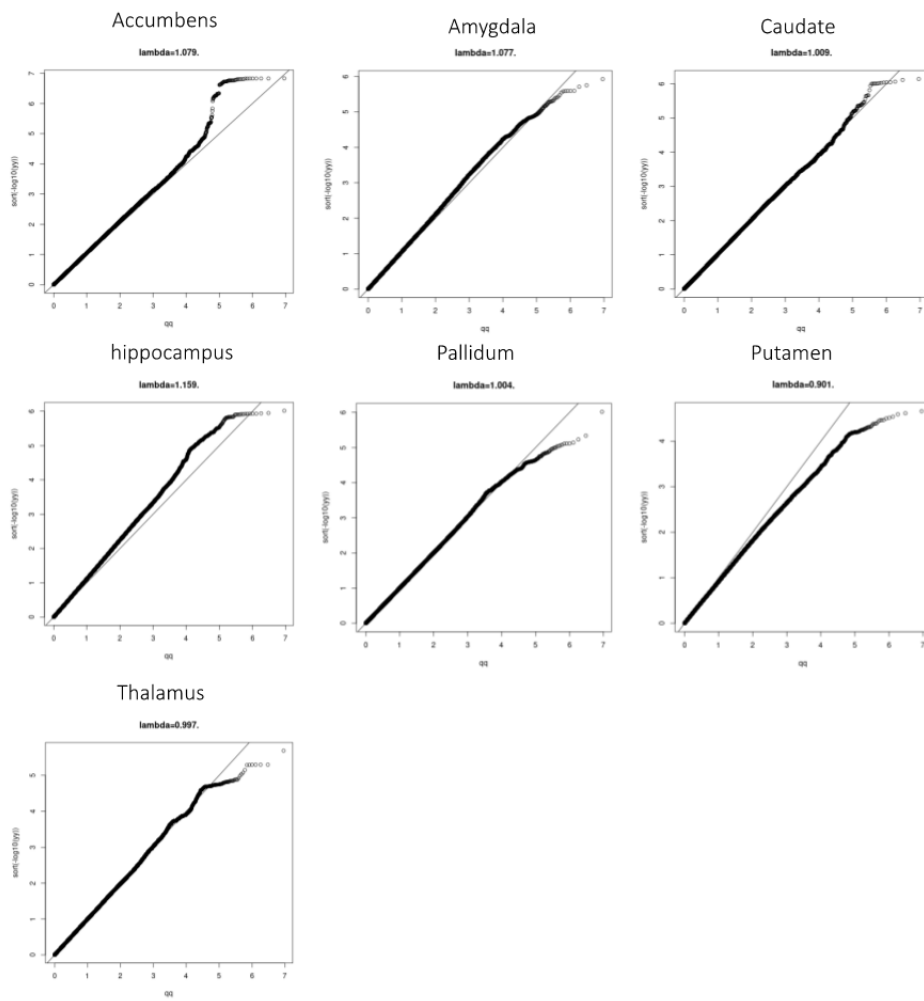
**Supplementary Figure 6** –Putamen PGS: The significance (**A**) and effect size estimate (**B**) of the PGS predicting putamen volume as a function of the threshold.



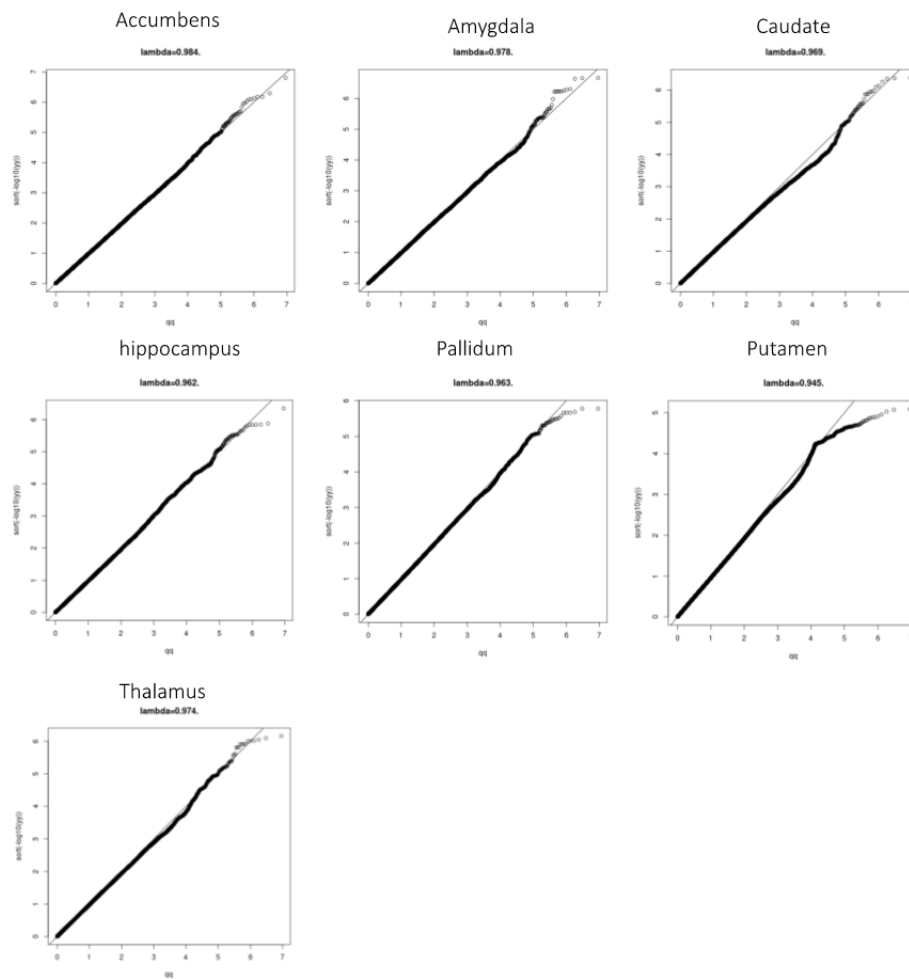
**Supplementary Figure 7** –Thalamus PGS: The significance (**A**) and effect size estimate (**B**) of the PGS predicting thalamus volume as a function of the threshold.



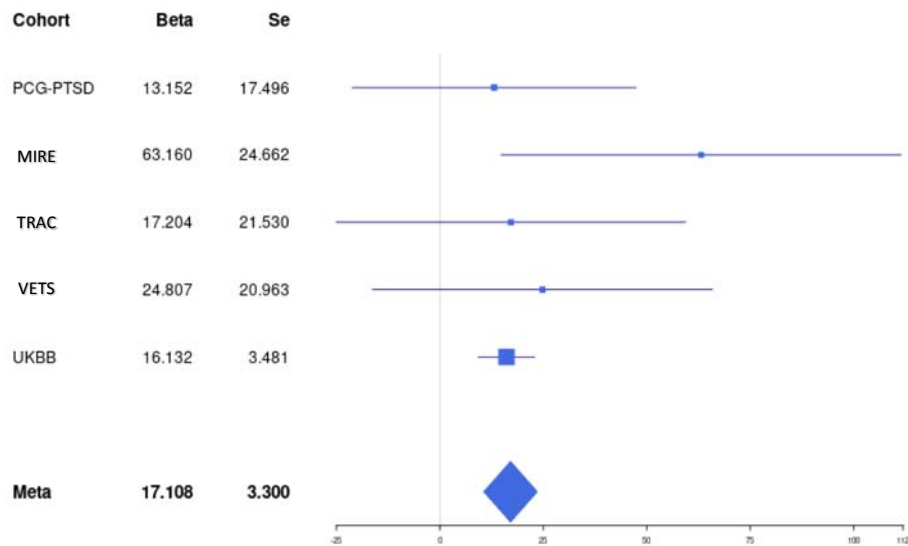
**Supplementary Figure 8:** QQ plots of the GxE GWASs of PTSD predicting subcortical volumes.



**Supplementary Figure 9:** QQ plots of the GxE GWAS of childhood trauma predicting subcortical volumes.



**Supplementary Figure 10:** Forest plots of the effect of the GxE interaction between rs4702973 and CT on amygdala volume. Both volume has been standardized (mean=0, SD=1). (Abbreviations: Meta=meta-analysis, PGC-PTSD=Psychiatric Genetics Consortium-Posttraumatic Stress Disorder, TRAC=Translational Research Center for TBI and Stress, VETS=Vietnam Era Twin Study of Aging; MIRE= MIRE=Duke University and VA Mid-Atlantic Mental Illness Research Education and Clinical Center, UKBB=United Kingdom BioBank).



**Supplementary Table 1:** Methods for assessing subcortical volume, genotypes, and PTSD and Childhood Trauma (CT) across included cohorts.

| Cohort<br>(sub-cohort) | Scanner/<br>Software                       | Genotyping<br>Platform                                                                                           | Imputation<br>Method/Panel      | European<br>Ancestry<br>criterion | Additional Cleaning                                                                                              | PTSD<br>Severit<br>y<br>Assess<br>ment | PTSD (case/<br>control)<br>Criterion                 | CT<br>Assessment       |
|------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------------------|------------------------|
| PGC-PTSD               |                                            |                                                                                                                  |                                 |                                   |                                                                                                                  |                                        |                                                      |                        |
| (BETE)                 | Philips<br>Achieva                         | Illumina Human<br>OmniExpress 24 v1.1                                                                            | IMPUTE2/1000<br>Genomes Phase 3 | SNPweights                        | Call rate>95%, removed<br>individuals with sex<br>discordance, high inbreeding<br>coefficients, high relatedness | CAPS 4                                 | CAPS>45/DSM<br>4 criteria                            | ETI                    |
| (DEFE)                 | Siemens<br>TimTrio                         | Illumina PsychChip                                                                                               | IMPUTE2/1000<br>Genomes Phase 3 | SNPweights                        | Call rate>95%, removed<br>individuals with sex<br>discordance, high inbreeding<br>coefficients, high relatedness | CAPS 4                                 | DSM criteria                                         | n/a                    |
| (BRY2)                 | GE Signa                                   | Illumina PsychArray                                                                                              | IMPUTE2/1000<br>Genomes Phase 3 | SNPweights                        | Call rate>95%, removed<br>individuals with sex<br>discordance, high inbreeding<br>coefficients, high relatedness | CAPS 4                                 | DSM criteria                                         | n/a                    |
| (KMCT)                 | Philips<br>Achieva/<br>Siemens<br>Tim Trio | Illumina PsychArray                                                                                              | IMPUTE2/1000<br>Genomes Phase 3 | SNPweights                        | Call rate>95%, removed<br>individuals with sex<br>discordance, high inbreeding<br>coefficients, high relatedness | UCLA                                   | DSM 5 criteria<br>(highest of<br>parent or<br>child) | CTQ                    |
| TRAC                   | Siemens<br>Tim Trio /<br>Freesurfer<br>5.1 | Illumina<br>HumanOmni2.5-8                                                                                       | IMPUTE2/1000<br>Genomes Phase 1 | SNPweights                        | Call rate>95%, removed sex<br>discordance                                                                        | Diagnosti<br>c<br>interview            | DSM 4 criteria                                       | TLEQ                   |
| VETS                   | Siemens<br>TimTrio                         | Illumina<br>HumanOmniExpress-<br>24 v1.0A beadchips                                                              | MACH/ 1000<br>Genomes Phase 3   | SNPweights<br>and PCA             | Twin relationships confirmed                                                                                     | PCL-C                                  | DSM 3 criteria                                       | Adapted<br>Holmes-Rahe |
| MIRE                   | GE MR750                                   | Illumina<br>HumanHap650<br>beadchips/ Illumina<br>Human1M-Duo<br>beadchips/ Illumina<br>HumanOmni2.5<br>beadhips | IMPUTE2/1000<br>Genomes         | SNPweights<br>and PCA             | Call rate>98%, removed<br>duplicate and related<br>individuals, removed sex<br>discordance                       | DTS                                    | SCID for DSM<br>4                                    | CTQ                    |
| UKBB                   | Siemens<br>Skyra                           | Affymetrix Axiom                                                                                                 | HRC/UK10K                       | 4-means<br>clustering             | Removed related individuals,<br>high level of missingness or<br>heterozygosity, gender<br>discordance            | Adapted<br>PCL-S<br>and<br>PHQ9        | Cutoff score                                         | Adapted CTQ            |

Abbreviations: DEFE= Defining Essential Feature of Neural Damage - VA Minneapolis HealthCare System, Minneapolis MN USA; PGC-PTSD=Psychiatric Genetics Consortium-Posttraumatic Stress Disorder; TRAC= Translational Research Center for TBI and Stress, Boston VA HealthCare System, Boston MA USA; VETS=Vietnam Era Twin Study of Aging, San Diego VA Healthcare System, San Diego CA USA; MIRE=Duke University and VA Mid-Atlantic Mental Illness Research Education and Clinical Center the Study of Post-Deployment Mental Health Study, Durham NC USA; UKBB=United Kingdom BioBank; BRY2=Bryant2 Sydney Neuroimaging, University of New South Wales Australia, KMCT=Katie McLaughlin Child Trauma, Child Trauma and Neural Systems Underlying Emotion Regulation, University of Washington, Seattle WA USA; BETR= Biological Effects of Traumatic Experiences, University Medical Center, Utrecht Netherlands

**Supplementary Table 2 (A to G):** Significance of the model covariates in predicting subcortical volumes**A) Accumbens**

| <b>Cohort</b>   | <b>Covariate</b> | <b>Beta</b> | <b>P-Value</b> |
|-----------------|------------------|-------------|----------------|
| <b>MIRE</b>     | (Intercept)      | -0.12       | 0.61           |
|                 | Age              | 0.24        | 0.67           |
|                 | Age <sup>2</sup> | -0.37       | 0.52           |
|                 | Gender           | 0.13        | 0.59           |
|                 | ICV              | 0.52        | 1.82E-10       |
|                 | PC1              | 0.0038      | 0.96           |
|                 | PC2              | -0.012      | 0.87           |
|                 | PC3              | 0.036       | 0.62           |
|                 | PC4              | 0.064       | 0.37           |
| <b>PGC-PTSD</b> | (Intercept)      | 1.94        | 8.77E-24       |
|                 | Age              | -0.27       | 0.32           |
|                 | Age <sup>2</sup> | 0.05        | 0.85           |
|                 | Gender           | -0.1        | 0.39           |
|                 | ICV              | 0.46        | 1.76E-15       |
|                 | PC1              | 0.097       | 0.0087         |
|                 | PC2              | -0.014      | 0.7            |
|                 | PC3              | 0.018       | 0.62           |
|                 | PC4              | 0.026       | 0.48           |
|                 | siteMinneapolis  | -2.32       | 1.98E-44       |
|                 | siteNSW          | -2.26       | 9.20E-40       |
|                 | siteU Wash       | -2.2        | 6.25E-14       |
| <b>TRAC</b>     | (Intercept)      | -0.062      | 0.85           |
|                 | Age              | -0.32       | 0.55           |
|                 | Age <sup>2</sup> | 0.078       | 0.89           |
|                 | Gender           | 0.067       | 0.84           |
|                 | ICV              | 0.29        | 0.0006         |
|                 | PC1              | -0.018      | 0.81           |
|                 | PC2              | 0.019       | 0.8            |
|                 | PC3              | 0.077       | 0.3            |
|                 | PC4              | 0.035       | 0.64           |
| <b>UKBB</b>     | (Intercept)      | -0.082      | 2.03E-07       |

|             |                  |           |           |
|-------------|------------------|-----------|-----------|
|             | Age              | 0.28      | 0.06      |
|             | Age <sup>2</sup> | -0.61     | 4.36E-05  |
|             | Gender           | 0.17      | 7.28E-12  |
|             | ICV              | 0.37      | 1.17E-176 |
|             | PC1              | 0.0042    | 0.69      |
|             | PC10             | -0.0022   | 0.84      |
|             | PC2              | 0.011     | 0.3       |
|             | PC3              | -0.012    | 0.23      |
|             | PC4              | 0.026     | 0.013     |
|             | PC5              | -8.00E-05 | 0.99      |
|             | PC6              | -0.013    | 0.2       |
|             | PC7              | 0.018     | 0.091     |
|             | PC8              | 0.0011    | 0.92      |
|             | PC9              | -0.014    | 0.19      |
| <b>VETS</b> | (Intercept)      | -0.018    | 0.79      |
|             | Age              | -0.063    | 0.49      |
|             | Age <sup>2</sup> | -0.053    | 0.56      |
|             | ICV              | 0.16      | 0.0092    |
|             | PC1              | 0.0088    | 0.91      |
|             | PC2              | 0.0065    | 0.93      |
|             | PC3              | 0.055     | 0.45      |
|             | PC4              | -0.0066   | 0.93      |
|             |                  |           |           |

## B) Amygdala

| Cohort          | Covariate        | Beta   | P-Value  |
|-----------------|------------------|--------|----------|
| <b>MIRE</b>     | (Intercept)      | -0.34  | 0.13     |
|                 | Age              | -0.42  | 0.45     |
|                 | Age <sup>2</sup> | 0.38   | 0.5      |
|                 | Gender           | 0.38   | 0.11     |
|                 | ICV              | 0.52   | 1.34E-10 |
|                 | PC1              | -0.11  | 0.14     |
|                 | PC2              | 0.0083 | 0.91     |
|                 | PC3              | -0.037 | 0.6      |
|                 | PC4              | 0.072  | 0.31     |
| <b>PGC-PTSD</b> | (Intercept)      | 1.62   | 1.71E-17 |
|                 | Age              | -0.13  | 0.64     |
|                 | Age <sup>2</sup> | 0.022  | 0.93     |

|             |                  |         |          |
|-------------|------------------|---------|----------|
|             | Gender           | 0.25    | 0.034    |
|             | ICV              | 0.39    | 8.21E-12 |
|             | PC1              | 0.0031  | 0.93     |
|             | PC2              | -0.036  | 0.34     |
|             | PC3              | 0.0063  | 0.86     |
|             | PC4              | 0.042   | 0.25     |
|             | siteMinneapolis  | -2.34   | 1.27E-44 |
|             | siteNSW          | -2.05   | 7.02E-34 |
|             | siteU Wash       | -2.49   | 5.88E-17 |
| <b>TRAC</b> | (Intercept)      | -0.0081 | 0.98     |
|             | Age              | -0.11   | 0.84     |
|             | Age <sup>2</sup> | 0.033   | 0.95     |
|             | Gender           | 0.0086  | 0.98     |
|             | ICV              | 0.45    | 5.44E-08 |
|             | PC1              | -0.023  | 0.75     |
|             | PC2              | -0.001  | 0.99     |
|             | PC3              | 0.032   | 0.66     |
|             | PC4              | 0.14    | 0.046    |
| <b>UKBB</b> | (Intercept)      | -0.15   | 3.65E-24 |
|             | Age              | 0.71    | 2.14E-07 |
|             | Age <sup>2</sup> | -1      | 2.28E-13 |
|             | Gender           | 0.31    | 3.43E-41 |
|             | ICV              | 0.47    | <1E-176  |
|             | PC1              | -0.0034 | 0.72     |
|             | PC10             | 0.002   | 0.83     |
|             | PC2              | -0.008  | 0.4      |
|             | PC3              | -0.0027 | 0.78     |
|             | PC4              | 0.01    | 0.28     |
|             | PC5              | 0.012   | 0.22     |
|             | PC6              | -0.02   | 0.032    |
|             | PC7              | 0.014   | 0.15     |
|             | PC8              | -0.0028 | 0.77     |
|             | PC9              | -0.0034 | 0.72     |
| <b>VETS</b> | (Intercept)      | -0.016  | 0.81     |
|             | Age              | -0.037  | 0.68     |
|             | Age <sup>2</sup> | -0.02   | 0.82     |
|             | ICV              | 0.25    | 3.38E-05 |

|     |         |      |
|-----|---------|------|
| PC1 | -0.003  | 0.97 |
| PC2 | -0.0021 | 0.98 |
| PC3 | -0.0081 | 0.91 |
| PC4 | 0.0084  | 0.9  |

### C) Caudate

| Cohort          | Covariate        | Beta    | P-Value  |
|-----------------|------------------|---------|----------|
| <b>MIRE</b>     | (Intercept)      | -0.0096 | 0.96     |
|                 | Age              | -0.74   | 0.14     |
|                 | Age <sup>2</sup> | 0.44    | 0.38     |
|                 | Gender           | 0.011   | 0.96     |
|                 | ICV              | 0.56    | 7.51E-14 |
|                 | PC1              | -0.093  | 0.16     |
|                 | PC2              | 0.021   | 0.74     |
|                 | PC3              | 0.016   | 0.8      |
|                 | PC4              | 0.15    | 0.022    |
| <b>PGC-PTSD</b> | (Intercept)      | 0.94    | 1.28E-05 |
|                 | Age              | -1.13   | 0.00049  |
|                 | Age <sup>2</sup> | 0.89    | 0.0043   |
|                 | Gender           | -0.042  | 0.76     |
|                 | ICV              | 0.75    | 4.16E-26 |
|                 | PC1              | 0.063   | 0.15     |
|                 | PC2              | -0.039  | 0.37     |
|                 | PC3              | 0.065   | 0.12     |
|                 | PC4              | 0.056   | 0.2      |
|                 | siteMinneapolis  | -1.29   | 2.84E-13 |
|                 | siteNSW          | -0.78   | 1.87E-05 |
|                 | siteU Wash       | -1.69   | 6.62E-07 |
| <b>TRAC</b>     | (Intercept)      | 0.012   | 0.97     |
|                 | Age              | -1.25   | 0.015    |
|                 | Age <sup>2</sup> | 0.95    | 0.061    |
|                 | Gender           | -0.013  | 0.97     |
|                 | ICV              | 0.37    | 3.41E-06 |
|                 | PC1              | 0.064   | 0.36     |
|                 | PC2              | 0.023   | 0.73     |
|                 | PC3              | 0.021   | 0.76     |

|             |                  |         |          |
|-------------|------------------|---------|----------|
|             | PC4              | -0.079  | 0.26     |
| <b>UKBB</b> | (Intercept)      | 0.013   | 0.41     |
|             | Age              | -0.29   | 0.046    |
|             | Age <sup>2</sup> | 0.28    | 0.05     |
|             | Gender           | -0.029  | 0.24     |
|             | ICV              | 0.58    | <1E-176  |
|             | PC1              | 0.0089  | 0.38     |
|             | PC10             | 0.0049  | 0.63     |
|             | PC2              | 0.0073  | 0.47     |
|             | PC3              | 0.014   | 0.17     |
|             | PC4              | 0.0077  | 0.44     |
|             | PC5              | -0.0052 | 0.6      |
|             | PC6              | -0.0078 | 0.44     |
|             | PC7              | 0.0068  | 0.5      |
|             | PC8              | 0.01    | 0.3      |
|             | PC9              | -0.0081 | 0.42     |
| <b>VETS</b> | (Intercept)      | -0.0071 | 0.9      |
|             | Age              | 0.064   | 0.43     |
|             | Age <sup>2</sup> | 0.013   | 0.87     |
|             | ICV              | 0.51    | 1.19E-18 |
|             | PC1              | 0.016   | 0.8      |
|             | PC2              | -0.057  | 0.36     |
|             | PC3              | 0.032   | 0.6      |
|             | PC4              | -0.0021 | 0.97     |

#### D) Hippocampus

| Cohort          | Covariate        | Beta   | P-Value  |
|-----------------|------------------|--------|----------|
| <b>MIRE</b>     | (Intercept)      | 0.054  | 0.8      |
|                 | Age              | 0.52   | 0.33     |
|                 | Age <sup>2</sup> | -0.58  | 0.27     |
|                 | Gender           | -0.061 | 0.79     |
|                 | ICV              | 0.59   | 6.06E-14 |
|                 | PC1              | 0.071  | 0.31     |
|                 | PC2              | 0.019  | 0.78     |
|                 | PC3              | 0.11   | 0.11     |
|                 | PC4              | 0.11   | 0.095    |
| <b>PGC-PTSD</b> | (Intercept)      | 0.35   | 0.13     |

|             |                  |          |          |
|-------------|------------------|----------|----------|
|             | Age              | -0.42    | 0.23     |
|             | Age <sup>2</sup> | 0.22     | 0.5      |
|             | Gender           | 0.24     | 0.11     |
|             | ICV              | 0.56     | 2.17E-14 |
|             | PC1              | -0.03    | 0.52     |
|             | PC2              | 0.0054   | 0.91     |
|             | PC3              | 0.0091   | 0.84     |
|             | PC4              | 0.063    | 0.17     |
|             | siteMinneapolis  | -1.05    | 2.29E-08 |
|             | siteNSW          | 0.038    | 0.84     |
|             | siteU Wash       | -1.48    | 4.38E-05 |
| <b>TRAC</b> | (Intercept)      | -0.14    | 0.64     |
|             | Age              | -0.017   | 0.97     |
|             | Age <sup>2</sup> | -0.18    | 0.72     |
|             | Gender           | 0.15     | 0.64     |
|             | ICV              | 0.46     | 1.27E-08 |
|             | PC1              | 0.067    | 0.34     |
|             | PC2              | 0.073    | 0.28     |
|             | PC3              | 0.12     | 0.074    |
|             | PC4              | 0.11     | 0.11     |
| <b>UKBB</b> | (Intercept)      | -0.028   | 0.06     |
|             | Age              | 1.25     | 1.55E-18 |
|             | Age <sup>2</sup> | -1.54    | 5.14E-27 |
|             | Gender           | 0.059    | 0.014    |
|             | ICV              | 0.5      | <1E-176  |
|             | PC1              | 0.012    | 0.23     |
|             | PC10             | 0.0011   | 0.91     |
|             | PC2              | -0.0085  | 0.39     |
|             | PC3              | -0.00096 | 0.92     |
|             | PC4              | 0.016    | 0.11     |
|             | PC5              | 0.032    | 0.0011   |
|             | PC6              | -0.02    | 0.042    |
|             | PC7              | -0.00058 | 0.95     |
|             | PC8              | -0.004   | 0.69     |
|             | PC9              | 0.0074   | 0.46     |
| <b>VETS</b> | (Intercept)      | 0.0079   | 0.88     |
|             | Age              | -0.18    | 0.012    |

|                  |        |          |
|------------------|--------|----------|
| Age <sup>2</sup> | -0.13  | 0.073    |
| ICV              | 0.5    | 1.10E-19 |
| PC1              | 0.14   | 0.021    |
| PC2              | 0.053  | 0.35     |
| PC3              | -0.11  | 0.042    |
| PC4              | -0.086 | 0.13     |

#### E) Pallidum

| Cohort          | Covariate        | Beta   | P-Value  |
|-----------------|------------------|--------|----------|
| <b>MIRE</b>     | (Intercept)      | -0.63  | 0.0069   |
|                 | Age              | -0.42  | 0.46     |
|                 | Age <sup>2</sup> | 0.12   | 0.84     |
|                 | Gender           | 0.71   | 0.0045   |
|                 | ICV              | 0.3    | 0.00013  |
|                 | PC1              | -0.1   | 0.17     |
|                 | PC2              | 0.012  | 0.87     |
|                 | PC3              | 0.11   | 0.13     |
|                 | PC4              | 0.068  | 0.35     |
| <b>PGC-PTSD</b> | (Intercept)      | 0.76   | 0.0002   |
|                 | Age              | -0.51  | 0.1      |
|                 | Age <sup>2</sup> | 0.16   | 0.6      |
|                 | Gender           | 0.34   | 0.013    |
|                 | ICV              | 0.59   | 6.28E-19 |
|                 | PC1              | 0.044  | 0.29     |
|                 | PC2              | -0.028 | 0.51     |
|                 | PC3              | 0.033  | 0.41     |
|                 | PC4              | 0.048  | 0.25     |
|                 | siteMinneapolis  | -1.71  | 1.07E-22 |
|                 | siteNSW          | -0.67  | 9.99E-05 |
|                 | siteU Wash       | -0.69  | 0.031    |
| <b>TRAC</b>     | (Intercept)      | -0.22  | 0.47     |
|                 | Age              | -0.013 | 0.98     |
|                 | Age <sup>2</sup> | -0.11  | 0.83     |
|                 | Gender           | 0.23   | 0.46     |
|                 | ICV              | 0.44   | 7.21E-08 |
|                 | PC1              | 0.033  | 0.64     |
|                 | PC2              | 0.074  | 0.28     |

|             |                  |         |          |
|-------------|------------------|---------|----------|
|             | PC3              | -0.0075 | 0.92     |
|             | PC4              | -0.05   | 0.47     |
| <b>UKBB</b> | (Intercept)      | -0.026  | 0.072    |
|             | Age              | 0.3     | 0.029    |
|             | Age <sup>2</sup> | -0.35   | 0.011    |
|             | Gender           | 0.055   | 0.017    |
|             | ICV              | 0.63    | <1E-176  |
|             | PC1              | 0.022   | 0.022    |
|             | PC10             | -0.0035 | 0.71     |
|             | PC2              | 0.013   | 0.18     |
|             | PC3              | 0.00013 | 0.99     |
|             | PC4              | -0.019  | 0.047    |
|             | PC5              | 0.004   | 0.67     |
|             | PC6              | 0.012   | 0.22     |
|             | PC7              | -0.011  | 0.23     |
|             | PC8              | 0.0093  | 0.32     |
|             | PC9              | -0.012  | 0.19     |
| <b>VETS</b> | (Intercept)      | -0.024  | 0.64     |
|             | Age              | 0.027   | 0.7      |
|             | Age <sup>2</sup> | 0.11    | 0.1      |
|             | ICV              | 0.58    | 9.88E-26 |
|             | PC1              | -0.03   | 0.58     |
|             | PC2              | -0.018  | 0.74     |
|             | PC3              | -0.069  | 0.2      |
|             | PC4              | -0.012  | 0.83     |

#### F) Putamen

| Cohort      | Covariate        | Beta   | P-Value  |
|-------------|------------------|--------|----------|
| <b>MIRE</b> | (Intercept)      | -0.26  | 0.22     |
|             | Age              | -0.42  | 0.42     |
|             | Age <sup>2</sup> | 0.039  | 0.94     |
|             | Gender           | 0.29   | 0.2      |
|             | ICV              | 0.42   | 8.10E-09 |
|             | PC1              | -0.042 | 0.54     |
|             | PC2              | 0.045  | 0.49     |
|             | PC3              | 0.14   | 0.033    |
|             | PC4              | 0.042  | 0.53     |

|                 |                  |           |          |
|-----------------|------------------|-----------|----------|
| <b>PGC-PTSD</b> | (Intercept)      | 1.01      | 4.14E-07 |
|                 | Age              | -0.26     | 0.38     |
|                 | Age <sup>2</sup> | -0.11     | 0.7      |
|                 | Gender           | 0.37      | 0.0046   |
|                 | ICV              | 0.65      | 1.27E-23 |
|                 | PC1              | 0.042     | 0.29     |
|                 | PC2              | -0.03     | 0.46     |
|                 | PC3              | 0.027     | 0.48     |
|                 | PC4              | 0.092     | 0.02     |
|                 | siteMinneapolis  | -2.11     | 8.69E-34 |
|                 | siteNSW          | -0.73     | 1.04E-05 |
|                 | siteU Wash       | -2.24     | 1.49E-12 |
| <b>TRAC</b>     | (Intercept)      | -0.27     | 0.36     |
|                 | Age              | -0.18     | 0.72     |
|                 | Age <sup>2</sup> | -0.18     | 0.71     |
|                 | Gender           | 0.29      | 0.34     |
|                 | ICV              | 0.34      | 1.56E-05 |
|                 | PC1              | 0.1       | 0.15     |
|                 | PC2              | 0.069     | 0.3      |
|                 | PC3              | 0.037     | 0.59     |
|                 | PC4              | -0.003    | 0.96     |
| <b>UKBB</b>     | (Intercept)      | -0.13     | 1.27E-18 |
|                 | Age              | 0.042     | 0.77     |
|                 | Age <sup>2</sup> | -0.27     | 0.052    |
|                 | Gender           | 0.28      | 2.86E-31 |
|                 | ICV              | 0.48      | <1E-176  |
|                 | PC1              | 0.01      | 0.3      |
|                 | PC10             | -0.00074  | 0.94     |
|                 | PC2              | 0.0053    | 0.59     |
|                 | PC3              | -0.0085   | 0.38     |
|                 | PC4              | -0.012    | 0.21     |
|                 | PC5              | -6.30E-05 | 0.99     |
|                 | PC6              | -0.00084  | 0.93     |
|                 | PC7              | 0.0063    | 0.52     |
|                 | PC8              | 0.011     | 0.24     |
|                 | PC9              | -0.017    | 0.074    |
| <b>VETS</b>     | (Intercept)      | 0.0048    | 0.94     |

|                  |        |          |
|------------------|--------|----------|
| Age              | -0.013 | 0.88     |
| Age <sup>2</sup> | 0.048  | 0.58     |
| ICV              | 0.37   | 1.83E-10 |
| PC1              | 0.034  | 0.64     |
| PC2              | -0.031 | 0.66     |
| PC3              | 0.044  | 0.52     |
| PC4              | -0.055 | 0.43     |

#### G) Thalamus

| Cohort   | Covariate        | Beta    | P-Value  |
|----------|------------------|---------|----------|
| MIRE     | (Intercept)      | 0.036   | 0.86     |
|          | Age              | -0.12   | 0.81     |
|          | Age <sup>2</sup> | -0.14   | 0.78     |
|          | Gender           | -0.04   | 0.85     |
|          | ICV              | 0.59    | 1.91E-15 |
|          | PC1              | -0.06   | 0.35     |
|          | PC2              | -0.072  | 0.25     |
|          | PC3              | 0.024   | 0.7      |
|          | PC4              | 0.17    | 0.0065   |
| PGC-PTSD | (Intercept)      | 0.091   | 0.54     |
|          | Age              | 0.32    | 0.16     |
|          | Age <sup>2</sup> | -0.46   | 0.034    |
|          | Gender           | 0.11    | 0.27     |
|          | ICV              | 0.58    | 8.65E-31 |
|          | PC1              | -0.0054 | 0.86     |
|          | PC2              | 0.035   | 0.26     |
|          | PC3              | -0.025  | 0.4      |
|          | PC4              | 0.015   | 0.6      |
|          | siteMinneapolis  | 0.14    | 0.22     |
|          | siteNSW          | -0.72   | 1.47E-08 |
|          | siteU Wash       | -0.5    | 0.032    |
| TRAC     | (Intercept)      | -0.069  | 0.79     |
|          | Age              | 0.23    | 0.61     |
|          | Age <sup>2</sup> | -0.35   | 0.43     |
|          | Gender           | 0.074   | 0.79     |
|          | ICV              | 0.6     | 2.73E-15 |
|          | PC1              | -0.026  | 0.67     |

|             |                  |          |          |
|-------------|------------------|----------|----------|
|             | PC2              | 0.13     | 0.036    |
|             | PC3              | -0.0065  | 0.92     |
|             | PC4              | 0.021    | 0.73     |
| <b>UKBB</b> | (Intercept)      | -0.019   | 0.13     |
|             | Age              | -0.0071  | 0.95     |
|             | Age <sup>2</sup> | -0.31    | 0.0092   |
|             | Gender           | 0.04     | 0.051    |
|             | ICV              | 0.65     | <1E-176  |
|             | PC1              | 0.031    | 0.00016  |
|             | PC10             | -0.0034  | 0.68     |
|             | PC2              | -0.025   | 0.0023   |
|             | PC3              | 0.00098  | 0.91     |
|             | PC4              | -0.0064  | 0.44     |
|             | PC5              | 0.012    | 0.15     |
|             | PC6              | -0.0074  | 0.37     |
|             | PC7              | 7.20E-05 | 0.99     |
|             | PC8              | 0.013    | 0.12     |
|             | PC9              | -0.0016  | 0.84     |
| <b>VETS</b> | (Intercept)      | -0.05    | 0.36     |
|             | Age              | -0.14    | 0.056    |
|             | Age <sup>2</sup> | -0.0082  | 0.91     |
|             | ICV              | 0.55     | 2.06E-23 |
|             | PC1              | -0.088   | 0.15     |
|             | PC2              | 0.025    | 0.68     |
|             | PC3              | -0.08    | 0.18     |
|             | PC4              | -0.054   | 0.35     |

Abbreviations: PGC-PTSD=Psychiatric Genetics Consortium-Posttraumatic Stress Disorder, TRAC= Translational Research Center for TBI and Stress, VETS=Vietnam Era Twin Study of Aging; MIRE= MIRE=Duke University and VA Mid-Atlantic Mental Illness Research Education and Clinical Center, UKBB=United Kingdom BioBank.

**Supplementary Table 3:** Meta-analysis association between polygenic scores based on the Hibar et al. 2015 subcortical volume GWAS and corresponding subcortical volume (see Table 2 for hippocampus).

| Region    | Threshold | Beta  | P-value  |
|-----------|-----------|-------|----------|
| Accumbens | 0.4131    | 0.051 | 1.99E-07 |
| Amygdala  | 0.7431    | 0.040 | 0.13     |
| Caudate   | 0.0371    | 0.083 | 1.97E-18 |
| Pallidum  | 0.0001    | 0.024 | 0.0069   |
| Putamen   | 0.0001    | 0.064 | 1.70E-12 |
| Thalamus  | 0.0431    | 0.048 | 7.46E-10 |

**Supplementary Table 4:** Meta-analysis of the association of all subcortical volume PGSs with PTSD.

| Region      | Threshold | Beta        | P-value      |
|-------------|-----------|-------------|--------------|
| Accumbens   | 0.4131    | 0.015       | 0.79         |
| Amygdala    | 0.7431    | <b>0.14</b> | <b>0.011</b> |
| Caudate     | 0.0371    | 0.018       | 0.78         |
| Hippocampus | 0.8891    | 0.10        | 0.081        |
| Pallidum    | 0.0001    | -0.023      | 0.74         |
| Putamen     | 0.0001    | 0.037       | 0.50         |
| Thalamus    | 0.0431    | 0.11        | 0.12         |

**Supplementary Table 5.** Significance of GxE interactions between PGSs for subcortical volumes and PTSD and Childhood Trauma.

| Region & Score | Threshold | PS x PTSD    | PS x PTSD    | PS x CT | PS x CT |
|----------------|-----------|--------------|--------------|---------|---------|
|                |           | Beta         | P-value      | Beta    | P-value |
| Accumbens      | 0.4131    | 0.061        | 0.43         | -0.029  | 0.56    |
| Amygdala       | 0.7431    | 0.047        | 0.28         | -0.004  | 0.85    |
| Caudate        | 0.0371    | 0.073        | 0.10         | 0.077   | 0.41    |
| Hippocampus    | 0.8891    | <b>-0.10</b> | <b>0.027</b> | -0.039  | 0.10    |
| Pallidum       | 0.0001    | -0.011       | 0.83         | -0.040  | 0.086   |
| Putamen        | 0.0001    | 0.017        | 0.72         | 0.020   | 0.38    |
| Thalamus       | 0.0431    | -0.012       | 0.78         | -0.018  | 0.36    |

**Supplementary Table 6.** Top GxE GWAS associations for A) the hippocampus and amygdala, and B) other subcortical regions. Only the most significant variant per gene/region is reported.

| A | Region      | E    | Genes                                   | Marker         | CHR | POS         | Effect Allele | Alt. Allele | Beta   | P-Value  | Direction* |
|---|-------------|------|-----------------------------------------|----------------|-----|-------------|---------------|-------------|--------|----------|------------|
|   | Amygdala    | CT   |                                         | rs4702973      | 5   | 99,293,221  | a             | c           | 17.11  | 2.16E-07 | +++++      |
|   | Hippocampus | CT   |                                         | rs75859483     | 8   | 142,956,633 | a             | g           | -44.87 | 4.49E-07 | ----?      |
|   | Hippocampus | PTSD |                                         | rs35700850     | 3   | 8,116,965   | t             | tag         | -32.53 | 9.63E-07 | ---+?      |
|   | Hippocampus | PTSD |                                         | rs7235463      | 18  | 48,988,864  | t             | c           | -30.34 | 1.18E-06 | -----      |
|   | Amygdala    | PTSD | SNTG1                                   | rs147964805    | 8   | 51,219,220  | a             | at          | -35.29 | 1.19E-06 | --?-?      |
|   | Hippocampus | CT   | AC007204.1; ZNF253;<br>ZNF93            | rs1469702      | 19  | 19,970,787  | t             | g           | 36.38  | 1.43E-06 | ++?+?      |
|   | Amygdala    | CT   |                                         | rs10443966     | 10  | 26,637,408  | a             | g           | -25.76 | 1.61E-06 | --+?       |
|   | Hippocampus | PTSD | KIF7; PLIN1; TICRR                      | rs893725       | 15  | 90,128,223  | a             | c           | -29.45 | 1.64E-06 | +--+       |
|   | Amygdala    | PTSD | CHST11                                  | rs10861272     | 12  | 105,110,538 | a             | g           | 27.27  | 1.78E-06 | ?++?+      |
|   | Hippocampus | PTSD | ANO4                                    | rs7974164      | 12  | 101,358,282 | t             | c           | -36.82 | 1.83E-06 | +----      |
| B | Region      | E    | Genes                                   | Marker         | CHR | POS         | Effect Allele | Alt. Allele | Beta   | P-Value  | Direction* |
|   | Accumbens   | PTSD |                                         | rs2348408      | 4   | 160,398,945 | a             | c           | -7.54  | 1.47E-07 | ---+-      |
|   | Accumbens   | CT   | RP11-1085N6.3                           | rs17091959     | 14  | 57,157,766  | t             | c           | -8.61  | 1.56E-07 | --+?       |
|   | Caudate     | CT   | CSMD2                                   | rs71647939     | 1   | 34,040,737  | a             | g           | -46.65 | 4.17E-07 | ----?      |
|   | Thalamus    | CT   | ALG14; RWDD3; TMEM56;<br>TMEM56-RWDD3   | rs12755552     | 1   | 95,685,026  | a             | g           | -83.08 | 6.95E-07 | --+--      |
|   | Caudate     | PTSD | RGS13                                   | rs10489877     | 1   | 192,570,150 | a             | g           | -40.20 | 7.23E-07 | --+--      |
|   | Caudate     | PTSD | DHFR; MSH3; MTRNR2L2                    | rs3776967      | 5   | 80,002,350  | t             | c           | -33.66 | 9.04E-07 | -----      |
|   | Pallidum    | PTSD | BDP1; MCCC2                             | 5:70880199:G:T | 5   | 70,880,199  | t             | g           | -44.13 | 9.60E-07 | -?--?      |
|   | Caudate     | CT   |                                         | rs72430984     | 2   | 147,063,647 | a             | atg         | -34.86 | 1.12E-06 | ----?      |
|   | Pallidum    | CT   | LARS; PLAC8L1; POU4F3;<br>RBM27; SH3RF2 | rs68033861     | 5   | 14,567,1805 | ct            | c           | -17.60 | 1.67E-06 | +?-?-?     |
|   | Pallidum    | CT   | RBFOX1                                  | rs4375678      | 16  | 7,262,965   | t             | c           | -16.40 | 1.68E-06 | ----?      |

\*Direction: Direction of association for PCG-PTSD, UKBB, TRAC, VETS, MIRE respectively.

**Supplementary Table 7.** Nominally significant GxE candidate variant associations for A) the hippocampus and amygdala, and B) other subcortical regions.

| A | Paper             | E    | Region         | Gene               | Marker      | CHR | POS         | Effect Allele | Alt. Allele | Beta   | P-Value | Direction* |
|---|-------------------|------|----------------|--------------------|-------------|-----|-------------|---------------|-------------|--------|---------|------------|
|   | Nievergelt et al. | CT   | Hippocampus    | KAZN; TMEM51- AS1  | rs148757321 | 1   | 15,436,223  | ctgtg         | c           | 24.89  | 0.0030  | ++++?      |
|   | Stein et al.      | CT   | Hippocampus    | MAD1L1             | rs55789728  | 7   | 2,107,649   | a             | g           | -17.50 | 0.019   | ----?      |
|   | Stein et al.      | PTSD | Hippocampus    | CAMKV              | rs2777888   | 3   | 49,898,000  | a             | g           | -14.45 | 0.025   | ?--?+      |
|   | Stein et al.      | CT   | Amygdala       | CAMKV              | rs2777888   | 3   | 49,898,000  | a             | g           | 7.07   | 0.029   | ?+-?-      |
|   | Stein et al.      | PTSD | Hippocampus    | TSNARE1            | rs13262595  | 8   | 143,316,970 | a             | g           | -12.75 | 0.042   | +---       |
|   | Stein et al.      | PTSD | Hippocampus    | TSNARE1            | rs4129585   | 8   | 143,312,933 | a             | c           | -12.66 | 0.044   | +---       |
| B | Paper             | E    | Region         | Gene               | Marker      | CHR | POS         | Effect Allele | Alt. Allele | Beta   | P-Value | Direction* |
|   | Satizabal et al.  | PTSD | Pallidum       | RP11-624C23.1      | rs196807    | 8   | 24,682,649  | a             | g           | 12.46  | 0.0035  | ++++-      |
|   | Stein et al.      | PTSD | Caudate        | CRHR1              | rs242925    | 17  | 43,888,866  | t             | c           | -20.04 | 0.0050  | --+?       |
|   | Stein et al.      | PTSD | Putamen        | PIK3CG             | rs11773880  | 7   | 106,540,171 | t             | g           | -25.19 | 0.0082  | ----       |
|   | Stein et al.      | PTSD | Accumbens      | TSNARE1            | rs13262595  | 8   | 143,316,970 | a             | g           | -3.37  | 0.013   | ----+      |
|   | Stein et al.      | PTSD | Accumbens      | PIK3CG             | rs11773880  | 7   | 106,540,171 | t             | g           | -3.85  | 0.013   | +---       |
|   | Stein et al.      | PTSD | Accumbens      | TSNARE1            | rs4129585   | 8   | 143,312,933 | a             | c           | -3.35  | 0.014   | ----+      |
|   | Stein et al.      | PTSD | Accumbens      | TCF4               | rs35371867  | 18  | 53,193,027  | a             | g           | -3.33  | 0.018   | --+?       |
|   | Stein et al.      | PTSD | Accumbens      | CRHR1              | rs242925    | 17  | 43,888,866  | t             | c           | -3.21  | 0.021   | --+?       |
|   | Stein et al.      | PTSD | Caudate        | MAD1L1             | rs7680      | 7   | 1,855,531   | a             | g           | -21.39 | 0.023   | ----?      |
|   | Nievergelt et al. | PTSD | Accumbens      | PARK2              | rs9364611   | 6   | 162,163,506 | t             | c           | 4.86   | 0.025   | +++?       |
|   | Stein et al.      | CT   | Thalamus       | MAD1L1             | rs55789728  | 7   | 2,107,649   | a             | g           | -24.66 | 0.026   | ----?      |
|   | Stein et al.      | PTSD | Lat. Ventricle | MAD1L1             | rs10235664  | 7   | 2,086,814   | t             | c           | 243.77 | 0.029   | ++++       |
|   | Stein et al.      | PTSD | Lat. Ventricle | MAD1L1             | rs55789728  | 7   | 2,107,649   | a             | g           | 262.99 | 0.030   | +++?       |
|   | Satizabal et al.  | CT   | Putamen        | DLG2; LOC107984425 | rs1432054   | 11  | 83,260,225  | a             | g           | 17.63  | 0.040   | +++?       |
|   | Stein et al.      | CT   | Accumbens      | CAMKV              | rs2777888   | 3   | 49,898,000  | a             | g           | 2.80   | 0.041   | ?++?-      |

\*Direction: Direction of association for PCG-PTSD, UKBB, TRAC, VETS, MIRE respectively.