Correcting Systematic Inflation in Genetic Association Tests That Consider Interaction Effects
Application to a Genome-wide Association Study of Posttraumatic Stress Disorder

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IMPORTANCE Genetic association studies of psychiatric outcomes often consider interactions with environmental exposures and, in particular, apply tests that jointly consider gene and gene-environment interaction effects for analysis. Using a genome-wide association study (GWAS) of posttraumatic stress disorder (PTSD), we report that heteroscedasticity (defined as variability in outcome that differs by the value of the environmental exposure) can invalidate traditional joint tests of gene and gene-environment interaction.

OBJECTIVES To identify the cause of bias in traditional joint tests of gene and gene-environment interaction in a PTSD GWAS and determine whether proposed robust joint tests are insensitive to this problem.

DESIGN, SETTING, AND PARTICIPANTS The PTSD GWAS data set consisted of 3359 individuals (978 men and 2381 women) from the Grady Trauma Project (GTP), a cohort study from Atlanta, Georgia. The GTP performed genome-wide genotyping of participants and collected environmental exposures using the Childhood Trauma Questionnaire and Trauma Experiences Inventory.

MAIN OUTCOMES AND MEASURES We performed joint interaction testing of the Beck Depression Inventory and modified PTSD Symptom Scale in the GTP GWAS. We assessed systematic bias in our interaction analyses using quantile-quantile plots and genome-wide inflation factors.

RESULTS Application of the traditional joint interaction test to the GTP GWAS yielded systematic inflation across different outcomes and environmental exposures (inflation-factor estimates ranging from 1.07 to 1.21), whereas application of the robust joint test to the same data set yielded no such inflation (inflation-factor estimates ranging from 1.01 to 1.02). Simulated data further revealed that the robust joint test is valid in different heteroscedasticity models, whereas the traditional joint test is invalid. The robust joint test also has power similar to the traditional joint test when heteroscedasticity is not an issue.

CONCLUSIONS AND RELEVANCE We believe the robust joint test should be used in candidate-gene studies and GWASs of psychiatric outcomes that consider environmental interactions. To make the procedure useful for applied investigators, we created a software tool that can be called from the popular PLINK package for analysis.

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Genetic studies of psychiatric disorders often conduct association analyses that consider interactions with environmental exposures of interest. Most such interaction studies have used candidate-gene designs, but psychiatric genetics is increasingly interested in using single-nucleotide polymorphism (SNP) data from genome-wide association studies (GWASs) to perform genome-wide interaction analysis. For a candidate-gene study or GWAS interaction analysis, a popular analytic tool is a joint test that considers the combined effects of SNP and SNP-environment interaction on outcome. If interactions exist, then these joint tests can yield greater power for gene mapping relative to traditional testing of marginal SNP effects alone and can resolve replication failures of marginal SNP findings. Many joint tests of main and interaction effects exist and are implemented in popular statistical software packages, such as PLINK. Researchers have used such procedures successfully to identify SNPs associated with various complex traits.

Using joint interaction tests, we performed a genome-wide interaction study of psychiatric outcomes related to post-traumatic stress disorder (PTSD) because PTSD arises from the complex interplay of genetics and environment. The differential risk determining those who do vs those who do not develop PTSD is multifaceted, but it is in part genetic, with approximately 30% heritability for PTSD risk after trauma. Cornelis et al. provided an overview of genetic findings for PTSD but noted that several candidate-gene studies identified genetic variants that interact with trauma-specific environmental exposures to influence PTSD. For example, SNPs in the FKBP5 gene interact with childhood maltreatment measures to raise the risk of PTSD. Whereas the effect of an insertion-deletion polymorphism in SLC6A4 on PTSD susceptibility appears to be modified by trauma type and social environment. Thus, studying genetic risk in the presence of environmental factors is important for psychiatric disorders, such as PTSD.

Motivated by the candidate-gene interaction findings for PTSD, we performed a genome-wide interaction analysis using joint interaction tests in a GWAS of PTSD and psychiatric-related outcomes collected by the Grady Trauma Project (GTP). The GTP performed genome-wide genotyping of approximately 4000 individuals and further collected psychiatric phenotype measures using outcomes such as the modified PTSD Symptom Scale (PSS) and the Beck Depression Inventory (BDI). The GTP also collected trauma history information from participants using measures such as the Childhood Trauma Questionnaire (CTQ) and the Trauma Experiences Inventory (TEI). Using this GTP data set, we performed genome-wide interaction analyses of quantitative psychiatric outcomes in PLINK27 with a joint SNP interaction test that considered the main effect of the SNP and its interaction with an environmental exposure (CTQ or TEI). PLINK implements this joint test using a linear regression model that regresses the psychiatric outcome on the genetic and environmental predictors as well as other covariates (such as principal components to correct for population stratification).

The results of the PLINK analyses revealed some unexpected trends. Specifically, we observed substantial genome-wide inflation in our joint tests across different outcomes and environmental exposures. At the same time, we observed no genome-wide inflation in the corresponding marginal SNP tests of each outcome that ignored the environmental exposures. Initially, it seems counterintuitive that a joint analysis of SNP and SNP-environment interaction would demonstrate genome-wide inflation, but its marginal counterpart would not. Nonetheless, subsequent research revealed a source behind our findings. For each outcome analyzed, we observed that the variance of the outcome differed by levels of the environmental exposure considered in the interaction term of the joint test. The observation that the variance of an outcome differs among levels of the trauma exposure is known as heteroscedasticity, and the phenomenon violates an important assumption of linear regression that requires the variance of trait outcome conditional on predictors to be the same across individuals (defined as homoscedasticity). Such heteroscedasticity originating from the environmental exposures leads to bias in the joint test of SNP and SNP-environment interaction but does not affect the marginal SNP test. This issue, if ignored, can lead to invalidation of joint interaction tests in candidate-gene SNP studies and larger GWAS projects.

Fortunately, we can correct for the inflation in the traditional joint tests of quantitative outcomes by modifying these tests to incorporate robust SEs that are insensitive to heteroscedasticity. These robust errors are often referred to as Huber-White, sandwich, or heteroscedasticity-consistent errors and are standard analytic tools in econometric, political science, anthropomorphic, and biomarker studies to deal with misspecification of mean and variance assumptions in statistical models. Such errors also were considered previously in gene-environment interaction studies to handle misspecification of the underlying mean model and violation of the homoscedasticity assumption. We found that application of this robust joint test to our PTSD interaction analyzes resolved the systematic inflation that we observed in our original joint tests that used model-based SEs. We further illustrate the robust approach using simulated quantitative data under heteroscedasticity and homoscedasticity models; we observed that our robust approach (1) consistently provides valid inference in models that yield inflation for the traditional joint test of SNP and SNP-environment interaction and (2) has power similar to the traditional joint test when homoscedasticity actually holds. We therefore believe the robust joint test should be used in interaction studies to ensure valid findings in GWASs and candidate-gene studies of quantitative outcomes. To enable investigators to easily use these robust interaction tests in existing GWASs and candidate-gene studies, we implemented the approach as software that can run directly through the popular PLINK software package for genetic analysis.

Methods
The GTP GWAS of PTSD
The GTP completed detailed trauma interviews on a large collection of underserved adults (mean age, 40 years) with high rates of current and lifetime PTSD. Study participants were primarily female and of African American ancestry. The GTP collected...
Genome-wide Association Study of the Beck Depression Inventory in the Posttraumatic Stress Disorder if the underlying modeling assumptions hold; we wished to
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frequency less than 0.10 might not follow the assumed asymp-
cause an interaction test of a SNP with a minor allele fre-
other filtered the SNPs considered for analysis by requiring a
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sample consisted of 3359 individuals (978 men and 2381
SNP data and constructed principal components for each study
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sample, whereas the Omni1-Quad BeadChip interrogates
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4622 individuals using the HumanOmniExpress (N = 280)
The GTP performed genome-wide SNP genotyping of
4622 individuals using the HumanOmniExpress (N = 280)
and Omni1-Quad BeadChip (N = 4342) (Illumina Inc). The
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anxiety measured using the CTQ. We describe the construc-
tion of these phenotypes and trauma exposures in the eMethods
in the Supplement. The institutional review board at Emory Uni-
vation of the asymptotic distribution of the test statistic).
Joint analyses considered environmental exposures using the Childhood
Trauma Questionnaire (CTQ) and Trauma Experiences Inventory (TEI). A
denotes the inflation factor (defined as the median of the test statistic divided
by the median of the asymptotic distribution of the test statistic).

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sample, whereas the Omni1-Quad BeadChip interrogates
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participant (eMethods in the Supplement). After this process,
our sample consisted of 3359 individuals (978 men and 2381
women) genotyped for 634,838 SNPs. For this article, we fur-
ther filtered the SNPs considered for analysis by requiring a
marker to have a minor allele frequency of 0.10 or greater in the
sample. We imposed this minor allele frequency filter be-
cause an interaction test of a SNP with a minor allele fre-
quency less than 0.10 might not follow the assumed asymp-
totic distribution (and therefore be invalid), because of the
limited number of individuals possessing the minor allele, even
if the underlying modeling assumptions hold; we wished to

remove this potential confounding issue from our analysis. Af-
ter this additional filtering step, the final number of SNPs used
in this work decreased from 634,838 to 494,793.

Using our final sample, we first performed marginal SNP
analysis of the PSSInt and BDI in PLINK using a Wald test de-
erived from a linear regression model that regressed outcome on
SNP, adjusting for the effects of the top 10 principal com-
ponents, sex, and genotyping chip used (HumanOmniExpress or
Omnit-Quad BeadChip). We next performed joint analysis of SNP
and SNP-environment interaction for various combinations of
outcome (PSSInt or BDI) and environmental exposure (TEI or
CTQ) using the regression framework shown in equation 1 in the
eMethods in the Supplement. We again adjusted for the ef-
effects of the top principal components, sex, and genotyping chip.
We constructed the model-based and robust joint tests (shown
in equations 3 and 5, respectively, in the eMethods in the Supple-
ment). We performed these analyses within PLINK using an R
software plugin (eMethods in the Supplement).

Results

Application of Model-Based Joint Tests in the GTP Cohort
Figure 1 shows the quantile-quantile (QQ) plots for the model-
based joint analyses of SNP and SNP-environment interac-
tion with the BDI. For comparison, Figure 1 also includes the
QQ plot of the marginal SNP association results for BDI. Figure 1
clearly shows sizable inflation in P values in both joint tests
that we considered. To quantify this observation, we calcu-
lated the genome-wide inflation factor (λ) for each joint analy-
sis as the median of the observed joint tests divided by the me-
dian of a χ² random variable (which is the asymptotic
distribution of the joint Wald test under the null hypothesis).
This quantity is a variation of the genomic-control inflation
factor⁴⁹ often applied in GWASs. We observed a genome-
wide inflation factor λ = 1.21 for the model-based joint test of
SNP and SNP-CTQ interaction and λ = 1.07 for the model-
based joint test of SNP and SNP-TEI interaction. Applying a
variation of genomic control (by dividing each test statistic by
the estimated λ before calculating the P value) removed infla-
tion at the median but did not resolve the P value inflation in
these interaction tests for much of the distribution (eFigure 1
in the Supplement). In contrast, we found no such inflation in
marginal SNP tests of BDI (λ = 1.01; calculated as the median
of the observed marginal tests divided by the median of a χ²
random variable). The marginal result in Figure 1 did not ad-
just for the main effect of the environmental predictor (CTQ
or TEI); however, marginal analyses that adjusted for these
environmental outcomes yielded similar findings to the unad-
justed analyses (eFigure 2 in the Supplement).

Figure 2 presents analogous QQ plots for joint and mar-
ginal SNP analyses of the PSSInt. As with the BDI, the QQ
plots for the PSSInt demonstrate genome-wide inflation of the
joint SNP test (λ = 1.13 for the joint test of SNP and SNP-
CTQ interaction and λ = 1.07 for the joint test of SNP and
SNP-TEI interaction) but no such inflation for the marginal
SNP test (λ = 1.00). As above, application of genomic control
did not fully correct the P value inflation in the joint interac-

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SNP-TEI interaction) but no such inflation for the marginal
SNP test (λ = 1.00). As above, application of genomic control
did not fully correct the P value inflation in the joint interac-
Correcting Systematic Inflation in Genetic Tests

For the PSSint, we also observed statistically significant differences in the variance of the outcome across quartiles of the TEI and CTQ. We found the variance of the outcome was statistically different between the quartiles of the TEI and CTQ.

Joint analyses considered environmental exposures using the Childhood Trauma Questionnaire (CTQ) and Trauma Experiences Inventory (TEI). I denotes the inflation factor (defined as the median of the test statistic divided by the median of the asymptotic distribution of the test statistic).

We believe the bias we observed in the model-based joint SNP tests of main and interaction effect was due to heteroscedasticity of the outcome variables with respect to the trauma exposure in the GTP. We estimated the variance of the PSSint and BDI across quartiles of the TEI and CTQ and reported these estimates in the Table. For the BDI, we found the variance of the outcome was statistically different across quartiles of the TEI and CTQ ($P < 1 \times 10^{-4}$ for each combination using a Brown-Forsythe test of variance equality $^{30,31}$). For the PSSint, we also observed statistically significant differences in variance across the environmental exposures ($P < 1 \times 10^{-4}$ for each combination). Therefore, we conclude heteroscedasticity exists in the GTP data set.

Application of Robust Joint Tests in the GTP Cohort

Figure 3 shows the QQ plots from the GTP GWAS comparing the expected vs observed $P$ values (on a $-\log_{10}$ scale) for robust joint tests of SNP and SNP-environment interaction for the BDI and PSSint. We also provide the results for the analogous model-based joint test for comparison. For each joint analysis of SNP and SNP-environment interaction considered, the results clearly reveal that the use of the robust statistic nearly eliminates the systematic genome-wide inflation observed using the model-based statistic. For the BDI, we observed that the inflation of the joint test of the SNP and SNP-CTQ interaction decreased from $\lambda = 1.21$ when using the model-based statistic to $\lambda = 1.02$ when using the robust statistic. Similarly, genome-wide inflation of the joint test of the SNP and SNP-TEI interaction went from $\lambda = 1.07$ (model) to $\lambda = 1.01$ (robust). For the PSSint, we saw a similar reduction in the bias of the joint test of the SNP and SNP-environment interaction using the robust statistic. Once we applied the robust Huber-White variance estimators, we did not identify any joint tests that were genome-wide significant for the PSSint or BDI in the limited GTP data set.

Simulation Results

We further evaluated the model-based and robust versions of the joint tests using simulated data. We describe the simulation design in the eMethods in the Supplement. Figure 4 presents the QQ plots for the analysis of null data sets where neither SNP nor SNP-environment interaction effect influences phenotype. Figure 4 shows the expected vs observed $P$ values (on a $-\log_{10}$ scale) for joint testing of SNP and SNP-environment interactions under homoscedasticity and the 2 forms of heteroscedasticity. Under homoscedasticity, the results reveal that the model-based and robust joint tests have no systematic inflation under the null hypothesis. We expect the model-based joint test to be valid in this situation because, under homoscedasticity, the modeling assumptions required for valid inference using this statistic are fulfilled. However, under heteroscedasticity, we found that the model-based joint test led to conservative or anticonservative findings depending on the underlying simulation model. When the variance of individuals with the less common environmental exposure was 3-fold greater than the trait variance for individuals with the more common exposure, we observed that the model-based joint test had systematic inflation in $P$ values ($\lambda = 1.33$). In contrast, when the variance of individuals with the less common environmental exposure was 3-fold smaller than the trait variance for individuals with the more common exposure, we found that the model-based joint test had systematic inflation.
Joint analyses considered environmental exposures using the Childhood Trauma Questionnaire (CTQ) and Trauma Experiences Inventory (TEI). $\lambda$ denotes the inflation factor (defined as the median of the test statistic divided by the median of the asymptotic distribution of the test statistic). A, Joint test of the BDI (CTQ exposure); B, joint test of the BDI (TEI exposure); C, joint test of the PSSint (CTQ exposure); and D, joint test of the PSSint (TEI exposure).

Discussion

Many genetic association studies of psychiatric outcomes are interested in identifying genetic variants that act in conjunction with other environmental modifiers to influence phenotype. Such interactions can resolve replication failures of marginal SNP findings and explain missing heritability.\textsuperscript{7} We found that a traditional joint test of SNP and SNP-environment interaction for quantitative phenotypes can result in invalid findings when the assumption of homoscedasticity (which can be

atic deflation in $P$ values ($\lambda = 0.71$). Under both heteroscedasticity models, the robust joint test of SNP and SNP-environment interaction had no such inflation ($\lambda = 1.02$ for each heteroscedasticity model). In addition to evaluating null models, we also evaluated the model-based and robust joint tests in power simulations where an SNP or SNP-environment interaction influenced phenotype. As shown in the eResults and eFigure 3 in the Supplement, we observed that the robust joint test had equivalent power to the model-based joint test when homoscedasticity holds (such that the model-based test is valid).

Figure 3. Quantile-Quantile Plot of Observed $P$ Values vs Expected $P$ Values (on a $-\log_{10}$ Scale) for Joint Analyses of the Beck Depression Inventory (BDI) and the Intrusive Symptoms of the Posttraumatic Stress Disorder (PTSD) Symptom Scale (PSSint) in the PTSD Genome-wide Association Study Using Model-Based and Robust Variance Estimators
assessed using the Brown-Forsythe test of variance equality) is violated. This issue affects candidate-gene association studies and GWAS projects that consider interactions of continuous phenotypes. We illustrate this point using an existing GWAS of PTSD and simulated data. To resolve this bias in the traditional joint test, we used the idea of Voorman et al. to develop a robust joint test that uses Huber-White variance estimates to correct for heteroscedasticity and found that this approach corrects for the P value inflation (or deflation) seen in the model-based joint tests when heteroscedasticity exists while having equivalent power to the model-based test when homoscedasticity actually holds.

The observation that heteroscedasticity invalidates interaction tests has not been reported in psychiatric literature, and it is also underappreciated in nonpsychiatric genetic studies, with only a few association studies addressing and correcting for this issue using robust Huber-White variance estimators. For a binary environmental exposure, one could perform a valid joint interaction analysis in the presence of heteroscedasticity without the need of Huber-White SEs by performing a marginal genetic analysis stratified by exposure because, within each exposure stratum, outcome variance is constant. However, this procedure, unlike the Huber-White SEs, is not applicable to continuous environmental predictors, such as the CTQ and TEI score that are of interest in the GTP.

Our analyses focused on joint testing of continuous phenotypes using the model of Kraft et al; such joint tests are implemented in PLINK. Other joint interaction tests also exist and because these methods use model-based SEs that assume homoscedasticity, we expect them to be invalid under heteroscedasticity. Heteroscedasticity issues likely also invalidate the more exclusive test of the gene-environment effect alone as noted by Voorman et al. Using the traditional 1-df Wald test for testing gene-environment interaction exclusively, we observed that heteroscedasticity led to inflated P values in the analyses of the BDI and PSSint within the GTP (eFigure 4 in the Supplement). The use of robust Huber-White SEs eliminated this inflation.

Although heteroscedasticity affects the validity of joint SNP tests of quantitative outcomes, it does not affect the validity of binary outcomes (such as disease status) because the logistic regression model for the latter outcome does not make a homoscedasticity assumption of constant variance across individuals. Nevertheless, joint SNP tests of binary outcomes using model-based variance estimates can exhibit bias if the outcome mean is misspecified; for example, one assumes a linear effect of environment on the log of the odds of disease when the relationship is truly nonlinear. Voorman et al. and Tchetgen Tchetgen and Kraft noted this issue and reported that robust Huber-White SEs can be used to correct this problem and provide valid inference.

Conclusions

The robust joint test of interaction presented in this article corrects for the bias seen in the model-based joint tests when heteroscedasticity exists and remains powerful when
the homoscedasticity assumption actually holds. We therefore recommend the use of the robust joint test over the model-based joint test in psychiatric candidate-gene studies and GWASs as well as studies that use nonpsychiatric outcomes. To facilitate use by the public, we implemented our procedure as a software tool (http://genetics.emory.edu/labs/epstein/software) that can be run through the PLINK software package (http://pngu.mgh.harvard.edu/~purcell/plink/; eMethods in the Supplement). We note that robust estimators for interaction analysis also are available in the ProbABEL\textsuperscript{17} package implemented in the R programming language.

**ARTICLE INFORMATION**

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Author Contributions: Drs Almli and Epstein had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Almli, Binder, Bradley, Conneely, Epstein.

Acquisition, analysis, or interpretation of data: Almli, Duncan, Feng, Ghosh, Bradley, Ressler, Conneely, Epstein.

Drafting of the manuscript: Almli, Conneely, Epstein.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Almli, Feng, Ghosh, Epstein.

Obtained funding: Ressler, Epstein.

Administrative, technical, and material support: Duncan, Bradley, Ressler, Conneely.

Study supervision: Binder, Ressler, Conneely, Epstein.

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