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ORIGINAL ARTICLE

Polygenic risk for psychiatric disorders correlates with executive function in typical development

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Executive functions are a diverse and critical suite of cognitive abilities that are often disrupted in individuals with psychiatric disorders. Despite their moderate to high heritability, little is known about the molecular genetic factors that contribute to variability in executive functions and how these factors may be related to those that predispose to psychiatric disorders. We examined the relationship between polygenic risk scores built from large genome-wide association studies of psychiatric disorders and executive functioning in typically developing children. In our discovery sample (N = 417), consistent with previous reports on general cognitive abilities, polygenic risk for autism spectrum disorder was associated with better performance on the Dimensional Change Card Sort test from the NIH Cognition Toolbox, with the largest effect in the youngest children. Polygenic risk for major depressive disorder was associated with poorer performance on the Flanker test in the same sample. This second association replicated for performance on the Penn Conditional Exclusion Test in an independent cohort (N = 3681). Our results suggest that the molecular genetic factors contributing to variability in executive function during typical development are at least partially overlapping with those associated with psychiatric disorders, although larger studies and further replication are needed.

KEYWORDS
autism, depression, development, executive function, neuropsychology, polygenic risk scores

1 | INTRODUCTION

Executive functions encompass diverse cognitive abilities, including flexibility, inhibitory control, abstraction, fluency, selective attention and working memory. The quintessentially human instantiation of these skills not only sets us apart from the rest of the animal kingdom, but also plays an integral role in cognitive development. Perhaps because they exhibit protracted maturation, executive functions are particularly variable and vulnerable during childhood and adolescence. Furthermore, deficits in executive functioning are widely reported in psychiatric populations including those affected by attention deficit/hyperactivity disorder[1,2] (ADHD), autism spectrum disorder[1] (ASD), bipolar disorder[3] (BIP), major depressive disorder[4] (MDD), schizophrenia[5] (SCZ) and others.[6] Whether factors associated with risk for

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Data used in preparation of this article were obtained from the Pediatric Imaging, Neurocognition and Genetics (PING) study database (http://ping.chd.ucsd.edu). As such, the investigators within PING contributed to the design and implementation of PING and/or provided data but did not participate in analysis or writing of this report. A complete listing of PING investigators can be found at https://ping-dataportal.ucsd.edu/sharing/Authors10222012.pdf.

psychiatric disorders and resulting executive function disruptions also correlate with executive function performance during typical development remains unknown.

Heritability estimates are moderate to high, ranging from 0.29 to 0.76, for performance on many individual executive function tests.[7–9] Correlations in performance across tests are often summarized as having "unity and diversity"[10] to note both a task-domain general performance factor that cannot be explained by general cognitive abilities (unity) and also task-domain specific factors (diversity).[11,12] The heritability of executive function exhibits this same pattern. Twin and family studies suggest domain-general and domain-specific genetic contributions that appear separable from those affecting general cognitive abilities. Estimates of heritability for some of these latent factors has been as high as 1.[7–9] Contrary to quantitative genetics reports, molecular genetic studies are less revealing. A number of candidate genes have been proposed[13] but single gene studies provide mixed results and their reliability in small to moderate samples is questionable.[14] Genome-wide association studies (GWASs) aiming to scan all common genetic variants are also yet to add significantly to our understanding of individual differences in executive functioning.[15–18] It appears that the genetic architecture of executive functions, like other complex cognitive phenotypes,[19,20] is diffuse across very many variants (polygenic). Extremely large sample sizes for reliable single variant studies or alternative approaches will be needed to advance understanding of the molecular genetic contributions to executive functioning.

The use of polygenic risk scores (PRSs) is a powerful approach for gaining insights into the genetic architecture of cognitive phenotypes.[21,22] PRSs are quantitative scores that index, for each individual subject in a study sample, their aggregate genetic risk for a trait of interest. Specifically, a PRS is computed as the weighted sum counting all risk alleles for a selected set of single nucleotide polymorphisms (SNPs) carried by an individual. The weight used for each risk allele is the SNP log odds ratio estimated out of sample in a large GWAS of the given trait. PRSs are demonstrated to be powerful and reliable indicators not only for genetic contributions to single traits but also for genetic correlations between traits.[22] Associating psychiatric PRS with cognitive performance in healthy populations may advance our understanding of the overlap among genetic factors contributing to cognitive deficits emerging through psychiatric illness and those affecting variability in unaffected individuals.[23] Although PRSs do not provide the molecular specificity of single locus studies, they can provide important insights into broader aspects of genetic architectures. These broader relationships are important for informing newer analytic approaches exploiting functional hypotheses for improved power at finer scales.[24,25]

A growing body of work has begun investigating the association between psychiatric PRS and measures of cognitive performance in the general population. Higher ADHD PRSs have been associated with lower performance in IQ, educational achievement, working memory, and language skills in children[26–28] and lower IQ, educational attainment and verbal-numerical reasoning in adults.[28–30] A number of reports link increased SCZ PRS with lower IQ across the age range,[31] but also include negative correlations with attention, reaction time, memory and verbal numerical reasoning in adults[30,32] and language skills, verbal reasoning and social cognition in children.[33,34] In adults,[30] MDD and BIP PRS were negatively associated with reaction time and memory, while MDD was additionally associated with worse verbal-numerical reasoning. While reported PRS for ADHD, BIP, MDD and SCZ have typically produced negative correlations with cognitive performance, ASD is an exception. ASD PRS has been associated with *higher* IQ in children and adults[35,36] and *higher* educational attainment, memory and verbal fluency in adults.[30,35] Although interesting relationships are emerging the results are not yet definitive as inconsistencies exists[31,37] and only a limited number of domains have been considered.

Only 2 studies, to our knowledge, have examined the association between PRS for psychiatric outcomes and executive function, per se. Germine et al[33] considered the relationship between SCZ PRS and performance on a suite of tests, including 1 executive task. However, in a population of children ascertained from hospitals (Philadelphia Neurodevelopmental Cohort [PNC], described below) only associations with other domains were reported as significant (see above), but a nominally significant trend for SCZ PRS and speed performance on an executive task was observed. Benca et al[38] used a population sample of young adults to consider the relationship between PRS for 5 psychiatric disorders and 3 latent executive factors derived from performance on 9 executive tasks. Although the authors did not declare any findings significant study-wide, they did report nominally significant trends for MDD, ADHD and SCZ PRS. While the frequency of studies using PRS to probe the genetic architecture of cognition is growing, their associations with executive functions during typical development, in particular, remain speculative.

The aim of this study was to investigate the association between PRS for psychiatric disorders and executive function performance in typically developing children and adolescents. We used the results from GWAS of 5 psychiatric conditions (ADHD, ASD, BIP, MDD and SCZ) provided by the Psychiatric Genomics Consortium (PGC) to compute disorder-specific PRS. In our primary hypothesis test, we examined the aggregate effects of all psychiatric PRS and their interactions with age on executive function in 417 typically developing individuals from the Pediatric Imaging, Neurocognition and Genetics (PING) study. Because of "unity and diversity" described by quantitative genetic studies, we followed our primary analysis with descriptive, post hoc analyses. The goal of these analyses was to generate novel hypotheses about the potential specificity of the strongest disorder-specific PRS to each of 2 executive function tasks and their independence from effects on more general cognitive abilities. Finally, we selected our strongest findings for replication in a second, complimentary cohort, the PNC. We hypothesized that multiple PRSs would show associations with variability in executive functions, revealing plausible evidence for domain specificity. Importantly, we also explored the understudied, moderating effect of age.

2 | MATERIAL AND METHODS

2.1 | Psychiatric GWAS

The PGC published per SNP summary statistics for GWAS of 5 psychiatric conditions (https://www.med.unc.edu/pgc/results-and-downloads).

We obtained the statistics for ADHD[39]ADHD, ASD[40], BIP[41], MDD[42] and SCZ[43] GWAS. The numbers of cases/controls in each study was 2960/4519 (ADHD), 3303/3428 (ASD), 7481/9250 (BIP), 9240/9519 (MDD) and 34 241/45 604 (SCZ). The statistics provide per SNP odds ratios for 1 206 462, 9 499 590, 2 427 221, 1 235 110 and 9 444 231 SNPs, respectively. Odds ratios were natural log transformed (reconstituting the beta estimate from a logistic regression) for downstream analysis. Table 1 describes these data.

2.2 | The PING cohort

The PING study (http://pingstudy.ucsd.edu/Data.php)[52] created a comprehensive, publicly shared, data resource for studying standardized assessments of neurocognition, neuroimaging and genetics in typically developing children. Cross-sectional measurements on 1493 individuals ranging in age from 3 to 21 years were aggregated from sites across the United States. The cohort is described fully elsewhere.[52,53] Relevant to this study, subjects were excluded only for known history of neurological disorders, head trauma, preterm birth, severe psychiatric diagnosis (autism spectrum, SCZ or BIPs), intellectual disability, pregnancy, maternal daily drug or alcohol use during pregnancy or incompatibility with MRI (i.e. braces, pregnancy, claustrophobia, etc.). ADHD, general or specific learning disabilities, and/or depression, confirmed or suspected, were not exclusionary as these are fairly common in developing populations. However, no testing was conducted to screen for these conditions and therefore verification of a diagnosis or identification of additional participants who may have met criteria was not possible. Subjects were enrolled from the greater metropolitan areas of Baltimore, Boston, Honolulu, Los Angeles, New Haven, New York, Sacramento and San Diego. Each subject's medical, developmental, behavioral history, as well as family medical history and environment were obtained from parental questionnaires. Socioeconomic status (SES) was recorded as a 7-point scale rating parental education from “less than seven years” to “professional degree,” and a 12-point scale rating annual familial income from “less than $5,000” to “over $300 000.”

Neurocognitive performance was assessed using the NIH Toolbox Cognition Battery (NTCB, http://www.nihtoolbox.org/,[53,54]), a computerized battery designed for administration across the life span. The NTCB includes 8 subtests spanning 6 domains. In this study, we included the 2 measures of executive function, the Flanker Inhibitory Control and Attention test (Flanker) and the Dimensional Change Card Sort (DCCS) test, and the 2 language measures, the Picture Vocabulary and Oral Reading Recognition tests. Intraclass correlation coefficients of 0.92 for both the DCCS and Flanker tests,[55] 0.97 for Oral Reading Recognition, and 0.81 for Picture Vocabulary[56] indicate that all 4 NTCB tests show excellent test-retest reliability. Test scores were adjusted by Blom rank order normalization.[57] The executive function composite (EFC) score is the average of DCCS and Flanker scores and the verbal composite (VC) score is the average of the Picture Vocabulary and Oral Reading Recognition scores. Details on the Flanker and DCCS are in the Appendix S1, Supporting Information.

A total of 550 000 SNPs were genotyped from saliva samples using the Illumina Human660W-Quad BeadChip. Genotyped SNPs were imputed[58] to 6 492 742 expected allelic dosages. Imputations were performed with MaCH,[59] minimac[60] and phased haplotypes from European subjects in 1000 Genomes Project Phase 1.[61] Included dosages had r^2 quality >0.3, minor allele frequency >1%, per subject

TABLE 1 GWAS summaries

	Trait			GWAS			SNPs for PRS	
GWAS	h^2	h^2_{chip}	PRS r^2	Cases	Controls	SNPs	PING	PNC
ADHD[a]	0.76[f]	0.28[k]	0.001[l]	2960	4519	1 206 462	5363	–
ASD[b]	0.90[g]	0.17[k]	*0.008[m]	3303	3428	9 499 590	10 179	3787
BIP[c]	0.90[h]	0.25[k]	0.028	7481	9250	2 427 221	13 965	–
MDD[d]	0.31-0.42[i]	0.21[k]	*0.006	9240	9519	1 235 110	5622	3752
SCZ[e]	0.81[j]	0.23[k]	0.184	34 241	45 604	9 444 231	17 119	–

The heritability (h^2) and chip heritability (h^2_{chip}) are representative values for each disorder and suggest a large contribution of common genetic factors to disease liability. The within-trait PRS predictive power (PRS r^2) of the GWAS results varies approximately according to the sample sizes. *Note that the VE by PRS reported here are likely underestimates for the PRS used here. The ASD and MDD GWAS used in these studies to create PRS were subsets (40% and 80%, respectively) of the sample used for this study.

[a] Neale et al[39].

[b] Cross-Disorder Group of the Psychiatric Genomics[40].

[c] The Psychiatric GWAS Consortium Bipolar Disorder Working Group[41].

[d] Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium et al[42].

[e] Schizophrenia Working Group of the Psychiatric Genomics Consortium[43].

[f] Faraone and Mick[44].

[g] Freitag[45].

[h] Craddock and Sklar[46].

[i] Sullivan et al[47].

[j] Sullivan et al[48].

[k] Cross-Disorder Group of the Psychiatric Genomics Consortium et al[49].

[l] Hamshere et al[50].

[m] Anney et al[51].

missingness <1%, were autosomal, and had unambiguous strand alignment (A/T, C/G SNPs removed). Of the 1493 subjects, 1019 had acceptable NTCB, genotype and covariate data.

Analyses were restricted to PING subjects of European genetic ancestry (the same as the psychiatric GWAS) with no familial relationships. Genetic ancestry was determined using smartPCA routines in EIGENSTRAT[62] on the 1019 PING subjects combined with 1224 individuals with known genetic ancestry. Reference individuals sampled HapMap,[63] 1000 Genomes[61] and IntraGen[64] databases. Subjects with European genetic ancestry had scores on the first 10 principal components (PCs) of genetic similarity within 5 SDs of the mean of reference individuals with known European ancestry, leaving 463 subjects (Figure S1). Familial relatedness was determined from estimates of genome-wide identity by descent (IBD) among the remaining subjects using GCTA.[65] The 417 final subjects (191 female) were selected such that no pair had estimated IBD above 0.08 (Figure S2). The first 10 PCs recomputed with smartPCA on the final subjects were kept as covariates for residual genetic ancestry.[62]

PRSs were computed for each psychiatric GWAS following a standard approach[22] with parameters chosen to mimic a recent exemplar.[43] We intersected the 6 492 742 imputed SNPs in PING with each GWAS, randomly pruning the 5 sets so no pair of SNPs within 500 kb had r^2 linkage disequilibrium above 0.1. Only those with a *P* value <.05 in the GWAS were retained leaving 5363 (ADHD), 10 179 (ASD), 13 965 (BP), 5622 (MDD) and 17 119 (SCZ) SNPs. For each subject, we computed PRS as the log odds weighted sum of imputed SNP minor allele counts, for each psychiatric GWAS as the PRS. Computations were carried out with the "score" function in plink1.9.[66,67] Correlations among scores are in Figure S5.

Associations were performed using R version 3.1.[68] A "baseline" regression model predicted EFC from 23 covariates: age at neuropsychological testing, age squared, gender, 8 dummy variables for 9 acquisition sites, the 2 SES measures and 10 ancestry PCs. The "full" model included the 23 covariates plus all PRSs and their interactions with age and age squared (15 additional terms). Coefficient estimates are reported from the full model. Age, age squared and PRS were mean-centered prior to fitting. The primary hypothesis test was a likelihood ratio test (LRT) comparing the full model with the baseline model. For descriptive purposes, the covariates and PRS terms are divided into categories and presented hierarchically in Table 2 with *P* values from LRTs on nested hierarchical models.

Post hoc tests were conditional on significance in the primary test and presented to describe the effects of specific PRS along with age and age squared interactions. Variables with $P < .1$ in the full model were selected for follow-up. These analyses (Figure 1) depict the differences in variance explained (VE) (r^2) when adding the PRS or PRS plus interaction terms to the baseline model, with *P* values reported from nested LRTs. Analyses were repeated including VC in the baseline model according to the same procedure. Post hoc test *P* values are presented uncorrected for multiple testing. The tests are dependent on significance in the primary test, highly intercorrelated (i.e. the ASD PRS effect on DCCS with and without VC are essentially redundant tests) and meant to be interpreted as descriptive, generating novel hypotheses to be confirmed in independent studies.

2.3 | The PNC cohort

The PNC was accessed through dbGAP (accession number phs000607.v1.p1). Full descriptions of the cohort, subject acquisition and protocols are available elsewhere.[69,70] Briefly, 8741 subjects ages 8 to 21 were selected from approximately 50 000 recruited from the Children's Hospital of Philadelphia or affiliated clinics in the greater Philadelphia area. Inclusion required only an ability to consent and complete interviews and testing. A computerized structured screen modeled after the Kiddie-Schedule for Affective Disorders and Schizophrenia[71] was administered to each subject to assess the symptoms of potential psychopathology including mood, anxiety, behavioral, eating, psychosis or substance use issues. Subjects were given a medical rating derived from this interview to summarize the relative severity of symptom reports from none (0) or minor without CNS impact (1) to major (4). Clinical administered medical diagnoses for psychiatric conditions, however, were not available.

Neurocognitive abilities were assessed using the Penn Computerized Neurocognitive Battery.[69,72,73] Executive function was assessed by the Penn Conditional Exclusion Test (PCET; details in Supporting Information).[74] Direct measures of reliability are not currently available for the PNC version of the PCET. Scores from the Reading subtest from the Wide Range Achievement Test (WRAT Reading score) were also available for each subject.

TABLE 2 Primary hypothesis test

Model	Res. DF	RSS	DF	SS	R^2	P (LRT)	
Intercept only	416	384.5					
+Age	414	119.8	2	264.61	0.6883	3.16×10^{-199}	
+Gender	413	119.8	1	7.19×10^{-5}	0.6883	0.9874	
+Environment	403	111.1	10	8.71	0.711	4.7×10^{-4}	
+Genetic background	393	105.1	10	6.01	0.7266	0.0128	4.92×10^{-206}
+PRS main effects	388	102.1	5	3.07	0.7346	0.0397	
+PRS age interactions	378	97.6	10	4.5	0.7463	0.0654	0.0147
−Omitted PRS terms	389	101.3	−11	−3.72	0.7366		0.2117

Adding the joint effects of the 5 PRS (+PRS main effects, +PRS age interactions) is a significant improvement to the explanatory power of the model when compared to the baseline model (intercept, +age covariates, +gender covariates, +environmental covariates, +genetic background covariates). Breaking down the terms into themed groups suggests all covariates except gender are important aspects of the baseline model and the main effects of the PRS are more predictive than their age interactions. Removing the terms not considered for post hoc analysis (−omitted PRS terms) did not significantly reduce the fit of the model.

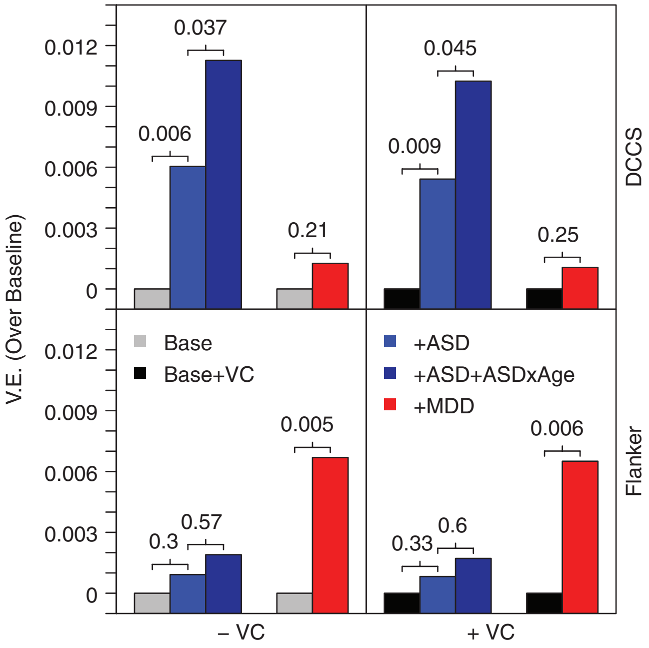

FIGURE 1 ASD and MDD PRS associate with different executive components in the PING cohort. Bar heights reflect increments in VE over the baseline (covariates only) model. Numbers indicate *P* values obtained from LRTs that compare the models sequentially, left to right. VE, variance explained; ASD, autism spectrum disorder PRS; MDD, major depressive disorder PRS; VC, verbal composite; DCCS, dimensional change card sort

Six arrays were used for genotyping: Affymetrix Human SNP Array 6.0 (*N* = 65, SNPs = 826 525), Affymetrix Axiom Genotyping Array (*N* = 711, SNPs = 517 744), Illumina Omni Array (*N* = 1653, SNPs = 699 239), Illumina Human 610 (*N* = 3702, SNPs = 480 247), Illumina Human Hap 550v1 (*N* = 548, SNPs = 522 609) and Illumina Human Hap 550v3 (*N* = 1861, SNPs = 488 715). We excluded subjects genotyped on the Affymetrix arrays for low numbers and low SNP overlap and subjects with the Illumina Human Hap 550v1 array for unresolvable artifacts. The same smartPCA and GCTA routines selected unrelated, European genetic ancestry subjects (Figure S3) and created ancestry covariate PCs. A total of 3681 subjects (1884 female) with 224 444 overlapping genotypes were used for replication. ASD and MDD PRS were computed according to the same protocol as above from 3787 and 3752 SNPs, respectively.

The PNC "baseline" model included 17 covariates: age at neuropsychological testing, age squared, gender, 4 dummy variables for 5 medical ratings and 10 genetic ancestry PCs. Age, age squared and PRS were centered prior to fitting. Replication tests followed the same procedure as in the discovery phase, comparing the fit of the PRS with baseline and interaction with PRS + baseline, sequentially. Coefficients are reported from the most saturated model. Analyses were repeated with the WRAT Reading score in the baseline model.

3 | RESULTS

Tested in aggregate, the PRS for ASD, ADHD, BIP, MDD and SCZ and their interactions with linear and quadratic age explained a small but significant proportion of variance in composite executive function among PING subjects (VE = 1.97%; LRT with 15 degrees of freedom (DF) *P* = .01; Table 2). Variables in the full model (Table S1) with *P* < .10 were chosen for follow-up: the main effect of MDD PRS (*β* = −0.0429, SE = 0.0167, *P* = .011), the main effect of ASD PRS (*β* = 0.0269, SE = 0.0107, *P* = .012) and the linear (*β* = 0.0210, SE = 0.0119, *P* = .078) and quadratic (*β* = −0.0009, SE = 0.0004, *P* = .064) age interactions with ASD PRS. Removing all PRSs but these from the full model did not result in a significant loss of fit, suggesting that results of the primary analysis are driven by the ASD, ASD × Age and MDD variables (VE = −1%, LRT with −11 DF *P* = .21; Table 2).

Comparative post hoc analyses examined the specificity of PRS effects across tasks and independence from more general cognitive abilities (Figure 1). ASD PRS and PRS-age interactions were significantly associated with performance on the DCCS task (PRS: VE = 0.6%, LRT with 1 DF *P* = .006; Interactions: VE = 0.5%, LRT with 2 DF *P* = .038), but not the Flanker (PRS: VE = 0.1%, LRT with 1 DF *P* = .31; Interactions: VE = 0.1%, LRT with 2 DF *P* = .57). An increased ASD PRS was associated with better performance on both the DCCS (*β* = 0.0325, SE = 0.0119), and although not significant, the Flanker (*β* = 0.0126, SE = 0.0125) in the ASD PRS and interactions models. The ASD age interaction suggests a larger effect in the younger subjects (Figure S6). The effect size and direction of the ASD PRS were essentially unchanged when adding VC to the baseline model for both the main effects of ASD PRS (DCCS: VE = 0.5%, LRT 1 DF *P* = .009; *β* = 0.0308, SE = 0.0118; Flanker: VE = 0.1%, LRT 1 DF *P* = .33; *β* = 0.0120, SE = 0.0125) and the age interactions (DCCS: VE = 0.5%, LRT 2 DF *P* = .046; Flanker: VE = 0.1%, LRT 2 DF *P* = .60).

The MDD PRS was significantly associated with Flanker performance (VE = 0.7%, LRT with 1 DF *P* = .005), but not DCCS (VE = 0.1%, LRT with 1 DF *P* = .21) where increased PRS coincided with decreased performance on the tasks (Flanker: *β* = −0.0542, SE = 0.0194; DCCS: *β* = −0.0236, SE = 0.0190). These associations were also essentially unchanged by including VC in the baseline model (DCCS: VE = 0.1%, LRT 1 DF *P* = .25; *β* = −0.0217, SE = 0.0188; Flanker: VE = 0.7%, LRT 1 DF *P* = .006; *β* = −0.0535, SE = 0.0194).

The power of our discovery tests is described in the Supporting Information Note and in Figures S10 and S11, and sensitivity analyses were conducted to examine the effect of reported ADHD and learning disability diagnoses on our results (Supporting Information Note, Tables S14-S19).

Replication (Figure 2) in the PNC showed a significant association between MDD PRS and performance on the PCET (VE = 0.1%, LRT with 1 DF *P* = .026) with increased MDD PRS corresponding to decreased executive function performance (*β* = −74.15, SE = 33.31). Neither the main ASD PRS effect (VE = 0%, LRT with 1 DF *P* = .99), nor the age interactions (VE = 0.01%, LRT with 2 DF *P* = .82) significantly associated with PCET performance. When including WRAT Reading scores into the baseline model, the main effect of MDD PRS remained significant (VE = 0.1%, LRT with 1 DF *P* = .034, *β* = −69.63, SE = 32.85), and the ASD main effect (VE = 0%, LRT with 1 DF *P* = .81) and interactions (VE = 0.01%, LRT with 2 DF *P* = .79) remained nonsignificant. Statistics from all models are provided in Tables S2-S13.

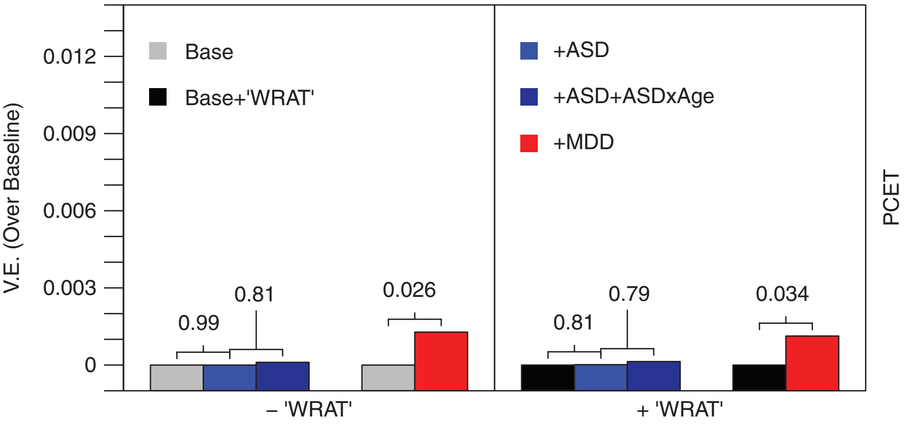

FIGURE 2 MDD PRS is associated with executive functioning in the PNC. Bar heights reflect increments in VE over the baseline (covariates only) model. Numbers indicate *P* values are obtained from LRTs that compare the models sequentially, left to right. VE, variance explained; ASD, autism spectrum disorder PRS; MDD, major depressive disorder PRS; WRAT, Wide Range Achievement Test, reading subtest; PCET, Penn Conditional Exclusion Test

4 | DISCUSSION

In this study, we report an initial association between PRS for MDD and executive functioning during typical development using performance on a test of inhibition (the Flanker task). We replicated this association in an independent developmental cohort via performance on a test of cognitive flexibility/shifting (the PCET). This across-domain replication may be supported by the "unity and diversity" model of executive functions where latent factor heritability analyses have suggested genetic effects on inhibition are redundant with a common executive factor.[11] Our result finds published support in a negative relationship between MDD PRS and inhibition using reaction time performance on a "Go/No-Go" task as reported by Hagenaars et al[30] in a sample of 111 484 adults. In a similar study, Benca et al[38] tested PRS for the same 5 disorders for associations with latent executive factors derived directly from the unity and diversity framework in a population sample of young adults that was similarly modest (n = 398). Although not declared significant at the experiment-wide threshold, they did report a nominal trend between the common executive factor and MDD PRS; however, it was in the opposite direction of our report. These results highlight a trend in the current literature describing the PRS effects on cognition where large samples often employ limited cognitive batteries and deeply phenotyped studies are limited by moderate sample sizes and power. While our result suggests a common, across-domain effect of genetic risk for major depression on executive functions during typical development, our sample size and the sparse published support necessitate further investigations.

We also report a positive association between ASD PRS and performance on the DCCS task in the PING cohort, however this effect did not replicate for performance on the PCET in the PNC, despite both targeting flexibility/shifting. In the only other study to directly consider this relationship, Benca et al[38] also reported null associations between ASD PRS and all 3 of common executive, updating specific and shifting specific latent factors. These mixed results are contrasted by more consistent reports in larger samples using PRS[30,35] and genetic correlations[30,36,75,76] suggesting a positive correlation between genetic risk for ASD and higher cognitive functioning in unaffected individuals; although a few null reports exist as well.[36,37]

Given these mixed results, our initial associations should be replicated and a few important features of the executive function study cohorts, in particular, could add context and motivate further research. First, PING, the PNC and Benca et al each employed different instruments to measure executive function and direct comparisons of the overlap in genetic contributions to each have not been performed. It is possible that the test-retest reliability of the PCET could be lower than for the battery used in PING,[55] reducing the power in our replication sample, although the most informative data to this point are currently lacking. "Task impurity" has been noted for measures of executive function[12] and quantitative genetics studies show cognitive tests targeting the same domain can have different sensitivities to underlying genetic effects.[11,77] For example, the positive correlation between general cognitive abilities and ASD PRS is present in our discovery data (Appendix S1; Figure S9) but the effect appears to be driven by a shifting/flexibility executive function component as measured by the DCCS. We cannot, however, rule out differing contributions of nontargeted domains among the studies. In this regard, the latent factor design of Benca et al[38] is the strongest. Second, each study targets a different age range, with PING extending to the youngest population where, for the ASD result, a trending PRS × age interaction suggests the effects are largest. The sensitivity of neuropsychological tests to particular subdomains likely changes with age[78] which could compound concerns of task impurity. As such, the differing ages of participants could obscure the expected homology across cohorts. Third, the sample sizes of each cohort are modest by current standards. In this context, the absence of an association should not be taken as a definitive null finding, although it is unlikely large effects exist. It remains possible that psychiatric risk for multiple disorders is associated with cognitive performance broadly or with varying specificity and future studies with wide-reaching cognitive batteries and larger samples will be needed to definitively characterize these effects. Finally, larger and more informative GWAS of psychiatric conditions are also needed. The sensitivity and specificity of PRS vary due to differences in sample size, power and reliability of odds ratios taken from training GWAS (Table 1) which also limits the power of current studies for defining the connections between genetic liability to psychiatric disorders and cognitive endophenotypes in the general population.

Broadly, our findings are consistent with well-established trends in research on learning (dis)abilities that suggest extensive overlap among the genetic factors contributing to normal variability in neurocognitive performance and those associated with learning disability diagnoses.[23] The presence of so-called Generalist Genes[23] among psychiatric disorders, both in terms of quantitative co-heritability[49] and shared molecular genetic factors[40] has been widely reported, as has extensive pleiotropy among cognitive abilities, most succinctly captured by the extremely high heritability of the "g" construct.[79] Relationships among genetic factors affecting variability in cognitive abilities in healthy individuals and those associated with psychiatric disease are only more recently emerging.[22,30,35,80] Because our results were not dependent on the presence of any disorder, we feel they can speak to 2 important themes in this discussion. First, it appears there is some overlap among molecular genetic factors contributing to differences in executive functioning and risk for disorders with executive functioning atypicalities. Second, perhaps executive brain systems dysfunctional in psychiatric disorders are components of a primary neurodevelopmental basis in which susceptibility arises, as opposed to targets of upstream dysfunctions defining the affected states.

Given the opposite directions for the PRS relationships observed in PING and described in previous reports, one could speculate that genetic and/or neurodevelopmental architectures creating ASD and MDD susceptibility may be qualitatively dissimilar. A negative association of MDD PRS and executive function performance is consistent with observations in affected individuals[4] and their unaffected family members.[81] ASD PRS, however, associates paradoxically in the opposite direction as reported for affected individuals,[1] unaffected family members[82] and healthy carriers of rare, large effect, often de novo copy number variants.[83] PRSs capture only a small portion of genetic liability for ASD (Table 1) and the directional inconsistency could resolve with more informative genetic instruments. An alternative hypothesis is that components of ASD risk captured by PRS (common polygenic risk) interact with rare genetic risk factors, altered neurodevelopment or environmental exposures to induce dysfunction in the ASD affected state. That ASD results from an imbalance or interaction among individually performance enhancing neurodevelopmental features has been proposed by others.[84]

Finally, new association methods prioritize single gene and single variant associations based on explicit pleiotropic hypotheses. For example, a proxy-phenotype approach used reports of genetic overlap between general cognitive abilities and educational attainment[24] to identify novel candidate associations for cognitive ability. Likewise, conditional approaches have suggested novel candidates by exploring genetic overlap of intuitively and unintuitively related phenotypes.[85–87] Our results suggest these approaches may aid studies of executive function, especially with smaller samples and extensive neurocognitive testing.

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Conflict of interest

Anders Dale is a founder of and holds equity interest in CorTechs Labs, La Jolla, CA and serves on its scientific advisory board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. All other authors declare no competing financial interests in relation to the work described.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supporting Materials

Supporting Note: Extended Methods
Supporting Note: Power Analysis
Supporting Note: ADHD and Learning Disabilities Sensitivity Analysis

Supporting Figure 1: PING Study Genetic Ancestry PCA, components 1 vs 2
Supporting Figure 2: PING Study Familial Relatedness

Supporting Figure 3: PNC Study Genetic Ancestry PCA, components 1 vs 2
Supporting Figure 4: PNC Study Familial Relatedness

Supporting Figure 5: Correlation among 5 psychiatric RPS in the PING Study

Supporting Figure 6: Visualized RPS effect: ASD-DCCS
Supporting Figure 7: Visualized RPS effect: MDD-Flanker
Supporting Figure 8: Visualized RPS effect: MDD-PCET

Supporting Figure 9: Replication of ASD-GC and Comparison with of ASD-DCCS

Supporting Figure 10: Power to detect aggregate PRS effects in PING cohort
Supporting Figure 11: Power to detect single PRS effects in PING cohort

Supporting Table 1: Full Primary Test Model Statistics

Supporting Table 2: ASD-DCCS without VC Model Statistics
Supporting Table 3: MDD-DCCS without VC Model Statistics
Supporting Table 4: ASD-DCCS with VC Model Statistics
Supporting Table 5: MDD-DCCS with VC Model Statistics
Supporting Table 6: ASD-Flanker without VC Model Statistics
Supporting Table 7: MDD-Flanker without VC Model Statistics
Supporting Table 8: ASD-Flanker with VC Model Statistics
Supporting Table 9: MDD-Flanker with VC Model Statistics

Supporting Table 10: ASD-PCET without WRAT Model Statistics
Supporting Table 11: MDD-PCET without WRAT Model Statistics
Supporting Table 12: ASD-PCET with WRAT Model Statistics
Supporting Table 13: MDD-PCET with WRAT Model Statistics

Supporting Table 14: Full Primary Test Model Statistics, including diagnosis variables
Supporting Table 15: Full Primary Test Model Statistics, censoring diagnoses individuals
Supporting Table 16: ASD-DCCS without VC Model Statistics, including diagnosis variables
Supporting Table 17: ASD-DCCS without VC Model Statistics, censoring diagnoses individuals
Supporting Table 18: MDD-Flanker without VC Model Statistics, including diagnosis variables
Supporting Table 19: MDD-Flanker without VC Model Statistics, censoring diagnoses individuals

Supporting Note: Extended Methods

NIH Toolbox Cognitive Battery: Dimensional Change Card Sort Task

The NTCB dimensional change card sort task (DCCS) measures cognitive flexibility and set-shifting in a computerized version of a test used to study executive function in children(1, 2). Participants are presented three picture stimuli on a touch screen monitor and instructed to touch the peripheral picture that matches the center target picture on a specified dimension (color or shape). Trials are presented sequentially in four blocks. Subjects begin with a training block to introduce the task. Next, a pre-switch block is administered consisting of five trials where subjects are told to match according to the same dimension as the last training block. A post-switch block follows and consists of five trials where subjects are told to match according to the other dimension. Finally, subjects perform a mixed block where the matching dimension is specified visually and audibly before each target appears. Mixed blocks consist of 40 dominant (same dimension as the post-switch block) and 10 non-dominant (same dimension as the pre-switch block) trials presented in a pseudorandom order. Performance is computed as the sum of a five-point accuracy and five-point reaction time score, with the reaction time score set to zero for subjects with < 80% accuracy.

NIH Toolbox Cognitive Battery: Flanker Inhibitory Control Test

The NTCB flanker inhibitory control and attention test (Flanker) measures inhibitory control in the context of selective attention and is a computerized adaptation of the Eriksen flanker test(3) adapted from the Attention Network Test(4). Subjects report the left-right orientation of a stimulus embedded centrally within a series of surrounding (flanker) stimuli. The flanker stimuli are either presented in the same orientation, congruous trials, or opposite orientation, incongruous trials. Subjects perform two blocks of 25 trials, 16 congruous and 9 incongruous, presented in a pseudorandom order, with the first block having fish stimuli and the second arrows. Like the DCCS, Flanker performance is recorded as the sum of a five-point accuracy and five-point reaction time score.

Penn Computerized Neurocognitive Battery: Penn Conditional Exclusion Test (PCET)

The PCET uses an "odd man out" paradigm in which subjects are presented four objects on a computer screen and instructed to select the one that does not belong. Objects vary on three sorting principles (shape, size or line type). Participants are not told which criterion to sort on, but are guided by feedback after each response. After ten consecutive correct responses the category is achieved and the sorting rule changes implicitly. Trials end when all three categories are achieved or a subject fails to achieve a category after 144 trials. Performance is scored as the proportion of correct responses multiplied by one plus the number of categories achieved. Age-adjusted performance a Reading subtest from the Wide Range Achievement Test-Fourth Edition (WRAT)(5) was used as the analogous measure to the VC in PING.

Replication and Comparison of ASD effects on General Cognitive Abilities

Previous reports have shown a positive correlation between ASD RPS and general cognitive abilities. This finding is reproduced in our data (Supporting Figure 9). We define general cognitive performance in PING as the average performance of all tests in the battery, a general cognitive composite (GC). To reproduce this finding, we fit our baseline covariate model with the GC as the dependent variable. We report the increase in variance explained by adding the ASD RPS and ASD RPS by age interactions to the baseline covariates only model. Significance tests were, as in the main analysis, LRTs comparing the baseline model to the baseline plus RPS model and baseline plus RPS model to baseline plus RPS plus RPS by age interactions model. To suggest specificity, we present the effect of ASD RPS on the general composite (GC), verbal composite (VC), fluid (performance) composite (FC), executive composite (EFC) and DCCS task alone (Supporting Figure 9, top panel), following the same model fitting and significance testing procedure as with the GC for each. The effect is noticeably the largest on the DCCS. Next, we asked if the effects on more general domains could be mediated by the DCCS or vice-versa (Supporting Figure 9, bottom panel). Here we recomputed each composite, removing the DCCS test from the averaging procedure for those domains which included it (GC*, FC*, EF*). For each composite, we re-ran the model testing procedure with the DCCS added to the baseline covariates model (GC* | DCCS, VC | DCCS, FC* | DCCS, EFC* | DCCS), displaying a test for independent effects of ASD that cannot be mediated by DCCS. We contrast this with the summaries of the ASD-DCC model fit including the modified GC* into the baseline model (DCCS|GC*). These models suggest that, in our data, the effect of ASD RPS on more general domains is completely mediated by its relationship with DCCS, but the opposite is not true. There appears to be some aspects of the ASD-DCCS relationship that are shared among other domains (unity), but also a significant proportion that are unique to DCCS (diversity).

Supporting Note: Power Analysis

The PING discovery sample is small relative to other investigations into common variant effects on complex traits such as performance on tests of cognitive function. Also, the variance explained by many of the Psychiatric PRS is quite modest, even when predicting the same trait in an out of sample test (Main Text Table 1). As such, we describe the power of our discovery sample to detect various effects sizes for our primary omnibus test for aggregate effects of multiple PRS and for individual tests of single PRS.

We used hypothetical F-tests to assess the power of our study following the functions implemented in the R package "pwr" (6, 7). F-tests and likelihood ratio tests (LRT) perform nearly identically in practice (although the LRT may have slightly more power) but the power calculations for F-tests may be easier to intuit as the variance explained (adjusted r^2) is a key parameter. We considered two scenarios to describe the power of the PING cohort in the context of this study: 1) mimicking the omnibus test estimating the significance of all PRS in aggregate and 2) mimicking a test for the effects of a single PRS.

In the first scenario, we investigated the power to detect a difference in the variance explained between two nested linear models in a sample of n=417. As was observed in the PING cohort, a baseline model was defined as including 23 covariates and an intercept (p1=24) that explained 71% of variance (adjusted r^2; r2.1). The full model included an additional 15 parameters (representing the PRS and PRS x Age terms; p2=39). The power of an F-test on the difference in variance explained by an expanded (full) model when compared to a nested baseline model is defined by the non-central F distribution specified in terms of the residual variance from the full model, the additional variance explained by the full model over the baseline, and the degrees of freedom used to estimate the two quantities. For various levels of increased variance explained (r2.d), power can be computed according to the following equations instantiated in R code:

```r
alpha <- 0.05                      # P-value Threshold for significance

n <- 417                           # sample size
p1 <- 24                           # parameters in model 1 (ie, "baseline" )
p2 <- 39                           # parameters in model 2 (ie, "expanded" or "full" )

r2.1 <- 0.7105792                  # Variance explained by the baseline model (adj. r^2)
r2.d <- r2.d                       # Additional Variance explained by the full model (adj. r^2)
                                          ( examined over multiple hypothetical values)

u <- p2-p1                         # degrees of freedom for additional variance explained
                                          ( ie, change in parameters )
v <- n-p2                          # degrees of freedom for the residual variance

f2 <- ( r2.d )/( 1-r2.1-r2.d )     # effect size = Explained Variance / Unexplained Variance
lambda <- f2 * ( u+v+1 )           # non-centrality parameter for the “true” F distribution
                                          where f2, u and v are as defined for the chosen
                                          alternative hypothesis

Fcrit <- qf( alpha, u, v, lower = FALSE ) # critical value for the F-test under the null
                                          # hypothesis of r2.d = 0, implying lambda = 0
                                          # ie, F, such that P( Fu,v >= F | Null is True ) = alpha

power <- pf( Fcrit, u, v, lambda, lower = FALSE ) # probability of observing F >= Fcrit under
                                                        a specific alternative hypothesis
                                                        defined by u, v, and r2.d
```

In the second scenario, we again considered the power to detect a difference in the variance explained by two nested linear models in a sample of n=417. The baseline model was the same as in scenario one, but the full model included only one additional parameter (a single PRS; p2=25). The power is estimated according to the same equations, replacing p2 with the new value. The resulting power curves for scenarios one and two are presented in Supporting Figures 10 and 11, respectively.

From these analyses, we see that our discovery cohort has greater than 50% power to detect aggregate PRS effects explaining more than 0.8% of variance and 80% power to detect aggregate effects that explain more than 1.36% of variance. Our study has greater than 50% power to detect a single PRS that explains more than 0.28% of variance and 80% power to detect a single PRS that explains more than 0.57% of variance.

Supporting Note: ADHD and Learning Disabilities Sensitivity Analysis

The PING sample was designed to collect a representative sample of children, more or less typically developing. Major psychiatric conditions (schizophrenia, bipolar disorder, autism spectrum disorders, mental retardation) and neurological disorders were conditions for exclusion, but more common, “milder” conditions, including a history of depression, ADHD, or general and/or specific learning disabilities were not exclusionary. A parental or self-report survey was administered for/to each participant that provided some details on neuropsychological history, including a reported history of stimulant medication, diagnosed attention problem and diagnosed learning problems. To probe the sensitivity of our results to sub-populations of subjects with ADHD or learning disabilities, we created two indicator variables. We combined subjects with a reported history of either stimulant medication or diagnosed attention problems into an ADHD-like group and we used reported history of diagnosed learning problems as a learning disabilities-like group. We repeated our three most important results, the primary aggregate test presented in Table 2 and Supporting Table 1, the DCCS-ASD result presented in Figure 1 and Supporting Table 2, and the flanker-MDD result presented in Figure 1 and Supporting Table 7, first, including the ADHD and learning disability group variables as covariates and, second, censoring these subjects all together.

Including the ADHD and learning disabilities variables improved the fit of the baseline, covariates only model for explaining the composite EF (change in variance explained (V.E.) = 0.0068, degrees of freedom (d.f.) = 2, likelihood ratio test (LRT) p = 0.0067). Thus, these groups have significant difference in executive performance. Reproducing the aggregate PRS test from Table 2 including the diagnosis variables, the variance in composite EF explained by aggregate PRS was essentially unchanged (original: V.E. = 0.0197, d.f. = 15, LRT p = 0.0147; including diagnosis group variables: V.E. = 0.0197, d.f. = 15, LRT p = 0.0119). Censoring these subjects removed 53/417 subjects, reducing the sample size by ~12%, and produced a slightly reduced VE estimate (censoring subjects with diagnosis: V.E. = 0.0173, d.f. = 15, LRT p = 0.0663). In both scenarios, individual regression estimates were highly consistent with the original result (Supporting Table 14-15).

Reproducing the ASD-DCCS results presented in Figure 1 and Supporting Table 2, including the diagnosis variables, the variance in DCCS explained by ASD PRS and ASD PRS by Age was also essentially unchanged (original: V.E. = 0.0113, d.f. = 3, LRT p = 0.0026; including diagnosis group variables: V.E. = 0.0114, d.f. = 3, LRT p = 0.0020). Censoring diagnosed subjects produced a slightly reduced VE estimate (censoring subjects with diagnosis: V.E. = 0.0084, d.f. = 3, LRT p = 0.0193). Again, in both scenarios, individual regression estimates were highly consistent with the original result (Supporting Table 16-17).

As with the previous two analysis sets, reproducing the MDD-Flanker results presented in Figure 1 and Supporting Table 7 and including the diagnosis variables, the variance explained in Flanker performance by MDD PRS was consistent (original: V.E. = 0.0067, d.f. = 1, LRT p = 0.0052; including diagnosis group variables: V.E. = 0.0066, d.f. = 1, LRT p = 0.0052). Censoring diagnosed subjects produced a slightly increased VE estimate (censoring subjects with diagnosis: V.E. = 0.0081, d.f. = 1, LRT p = 0.0032). Here as well, both scenarios produced individual regression estimates that were highly consistent with the original result (Supporting Table 18-19). Taken together, these sensitivity analyses suggest that our results are not driven by a sub-cohort of subjects with ADHD or learning disabilities.

Supporting References

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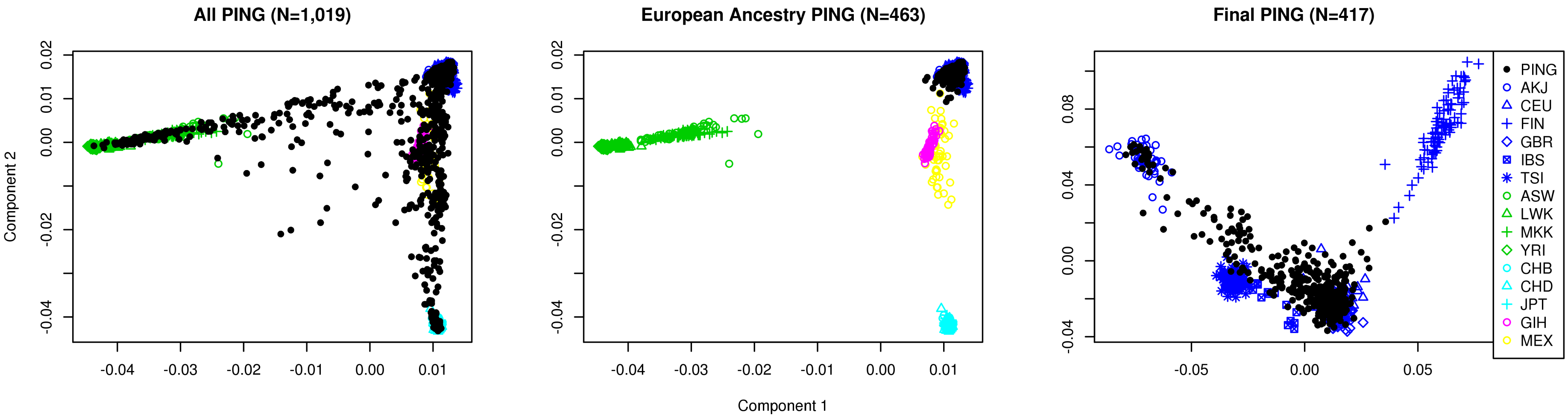
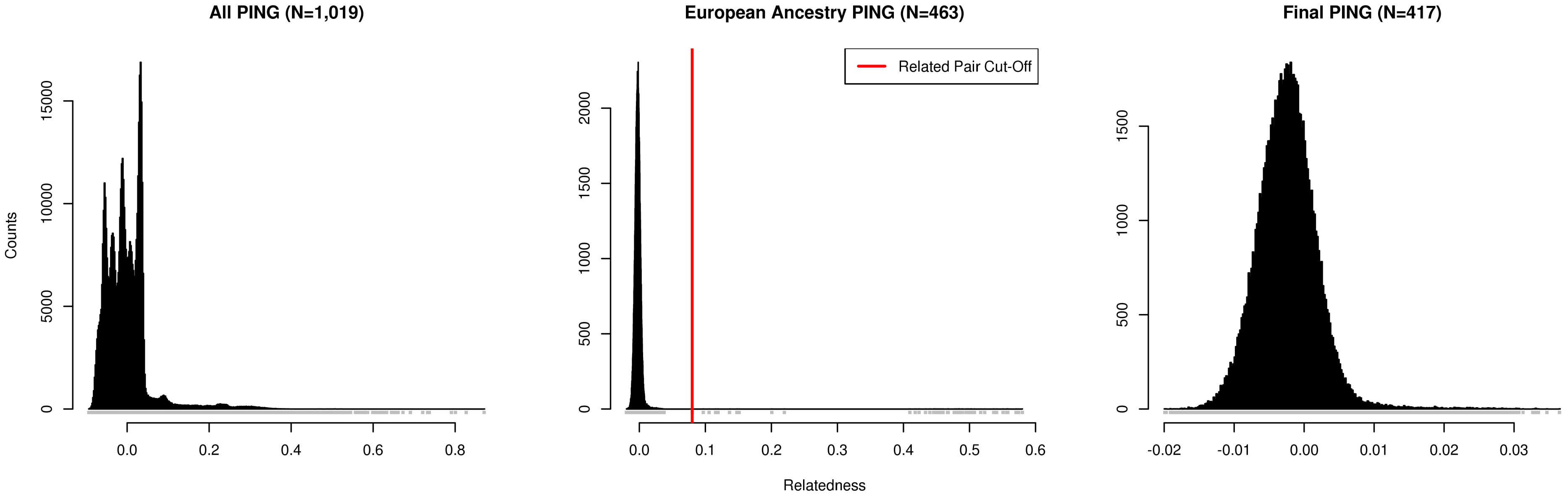
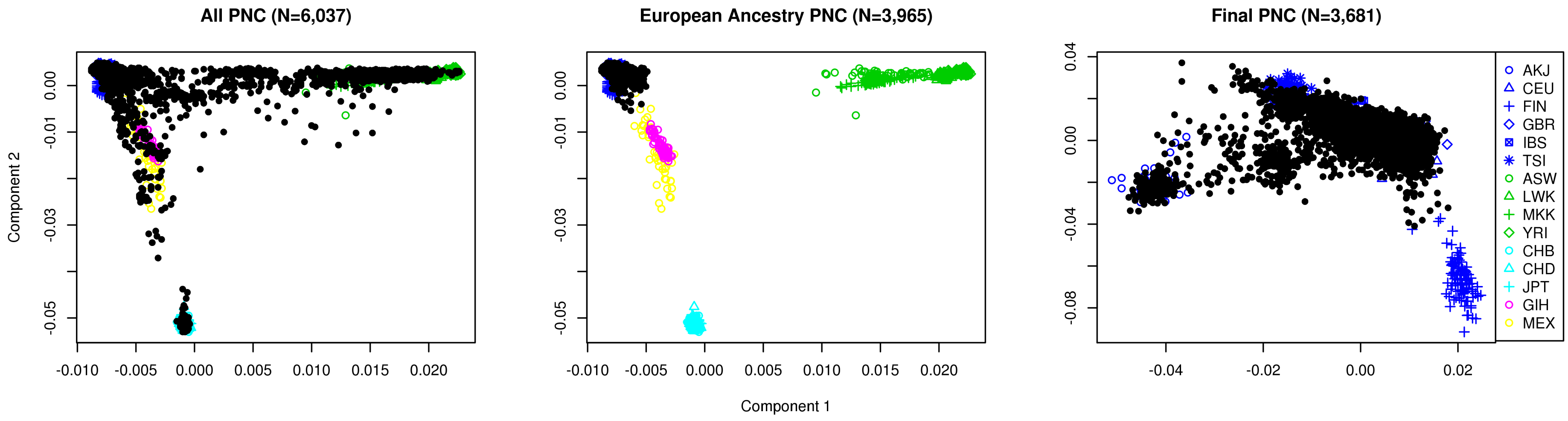


Supporting Figure 1: PING Study Genetic Ancestry PCA, PC1 vs PC2. The left plot is all PING subjects, the middle plot is all European subjects and the right plot shows the final individuals used for analysis. Reference individuals are color coded according to continent of ancestry. PING subjects are colored black. Ashkenazi Jewish ancestry (AKJ); American northern and western European ancestry (CEU); Finnish ancestry (FIN); Great Britain ancestry (GBR); Iberian ancestry (IBS); Tuscan ancestry (TBS); African American ancestry (ASW); Luhya Kenyan ancestry (LWK); Maasai Kenyan ancestry (MKK); Yoruba Nigerian ancestry (YRI); Han Chinese ancestry (CHB); American Han Chinese ancestry (CHD); Japanese ancestry (JPT); American Gujarati Indian ancestry (GIH); Mexican American ancestry (MEX).



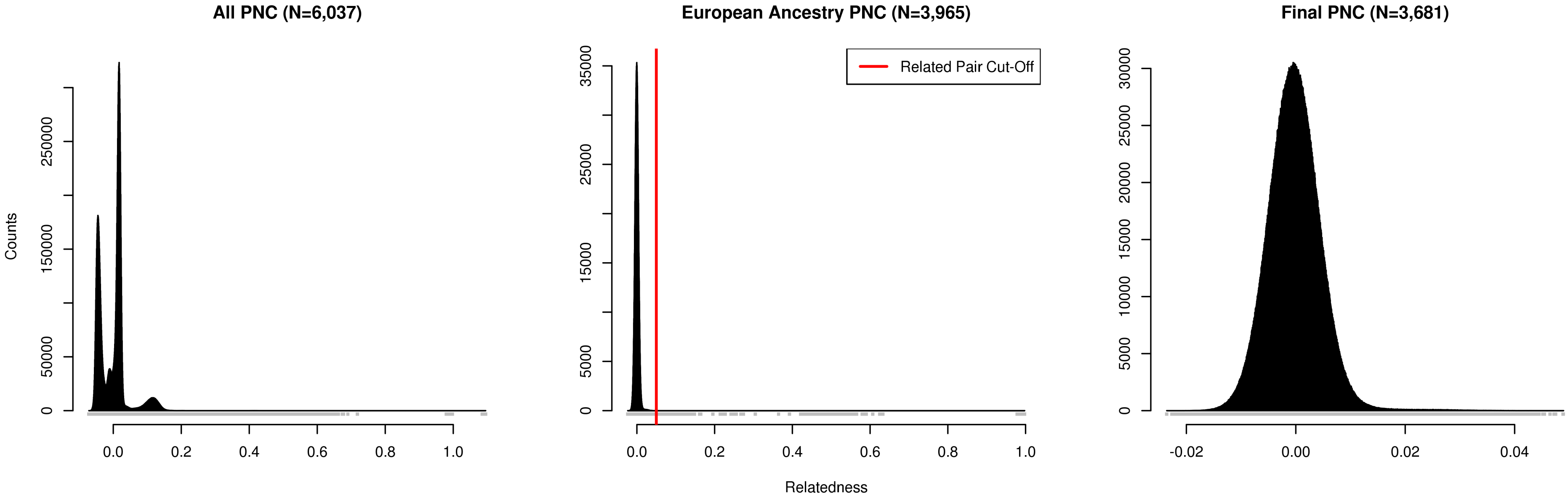
Supporting Figure 2: PING Study Familial Relatedness. The distributions of estimated IBD relationships among all, European ancestry and final subjects from the PING study.


All PNC (N=6,037)

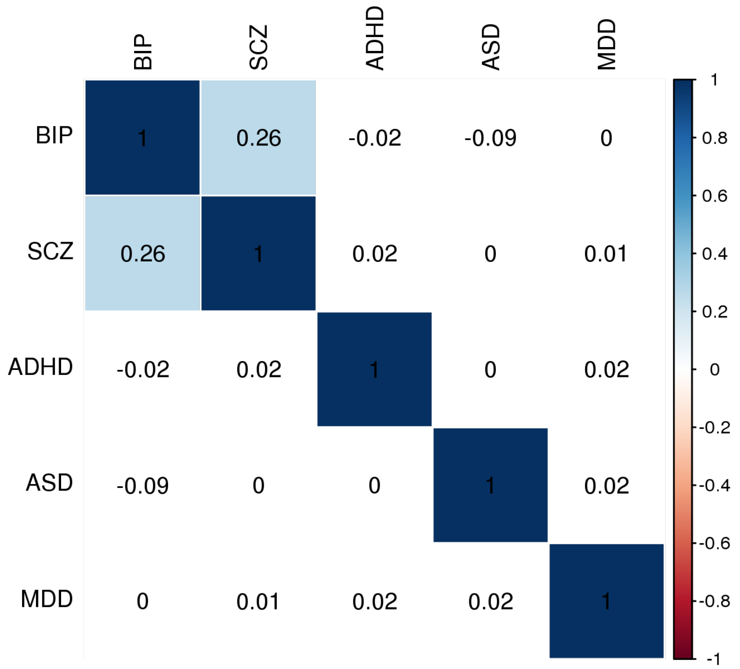
European Ancestry PNC (N=3,965)

Final PNC (N=3,681)

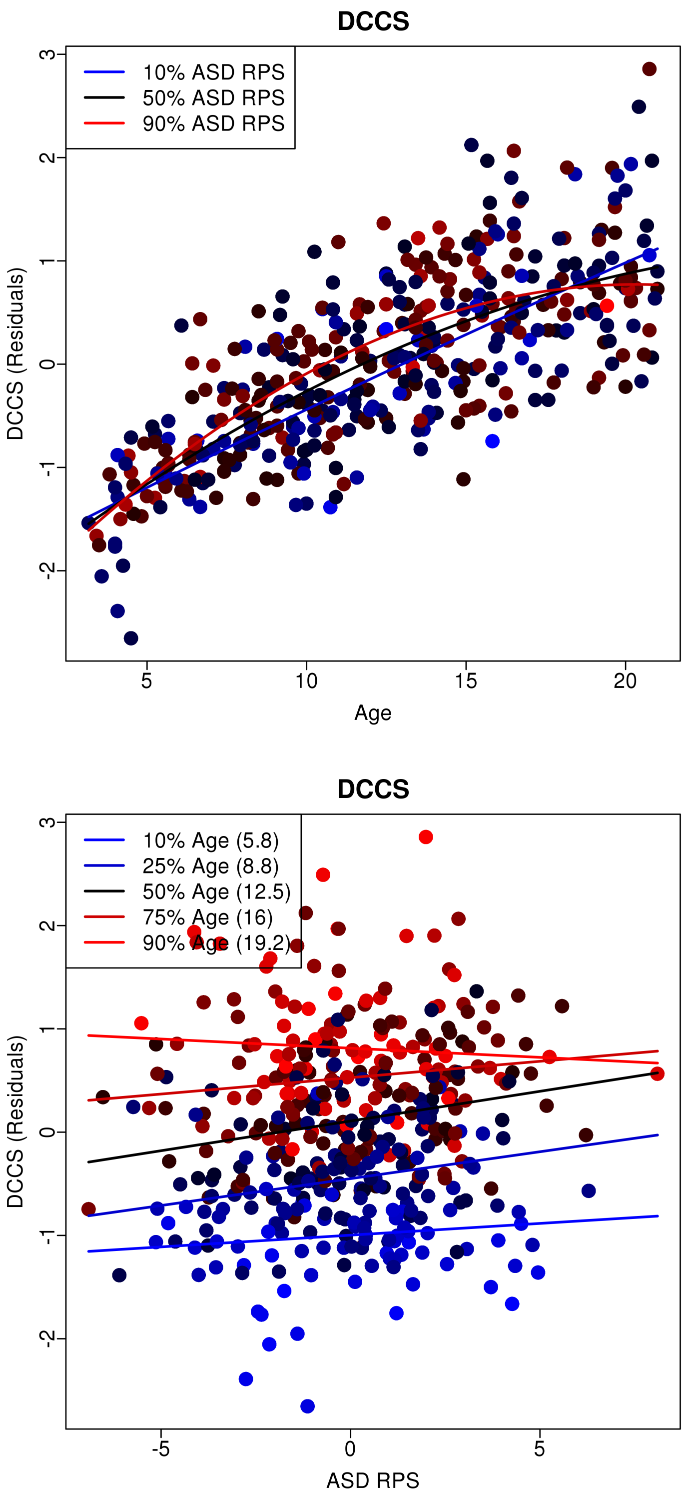
Supporting Figures 3: PNC Study Genetic Ancestry PCA, PC1 vs PC2



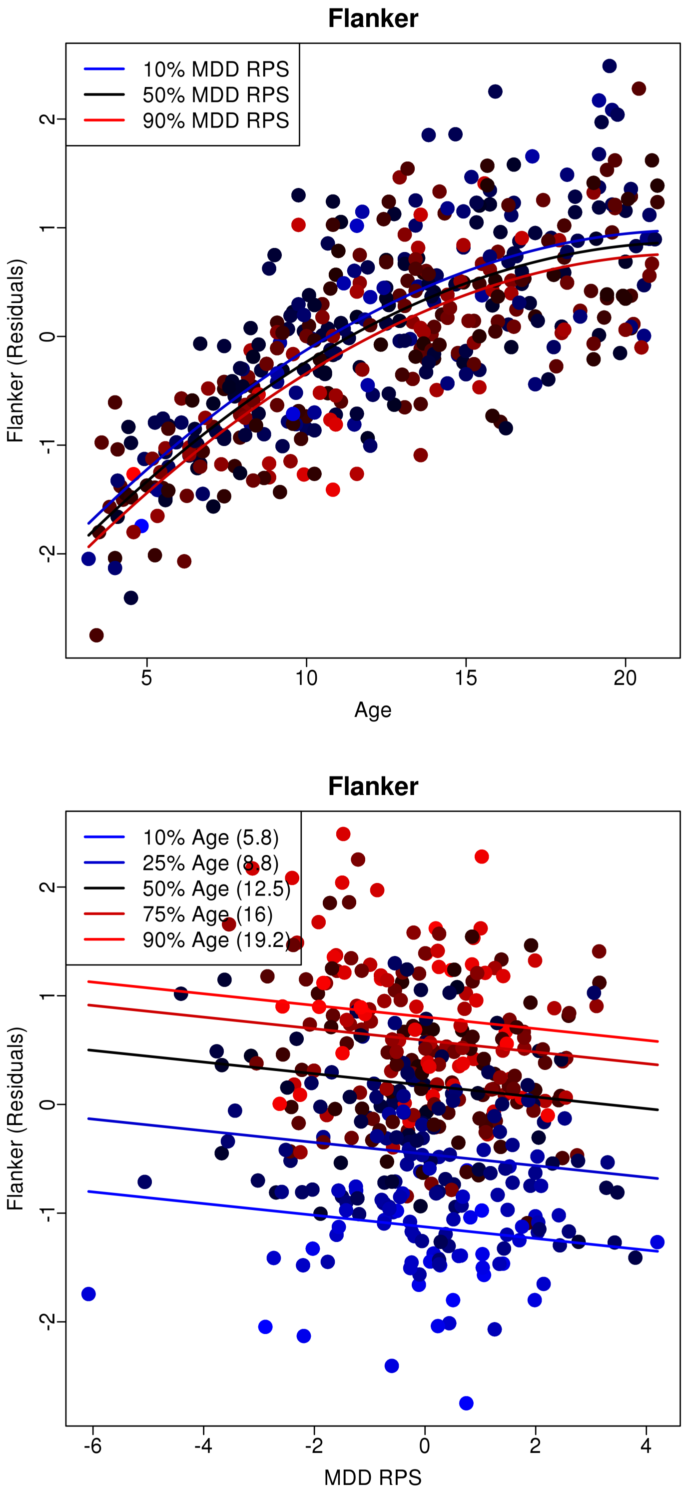
Supporting Figure 4: PNC Study Familial Relatedness. The distributions of estimated IBD relationships among all, European ancestry and final subjects from the PNC study.



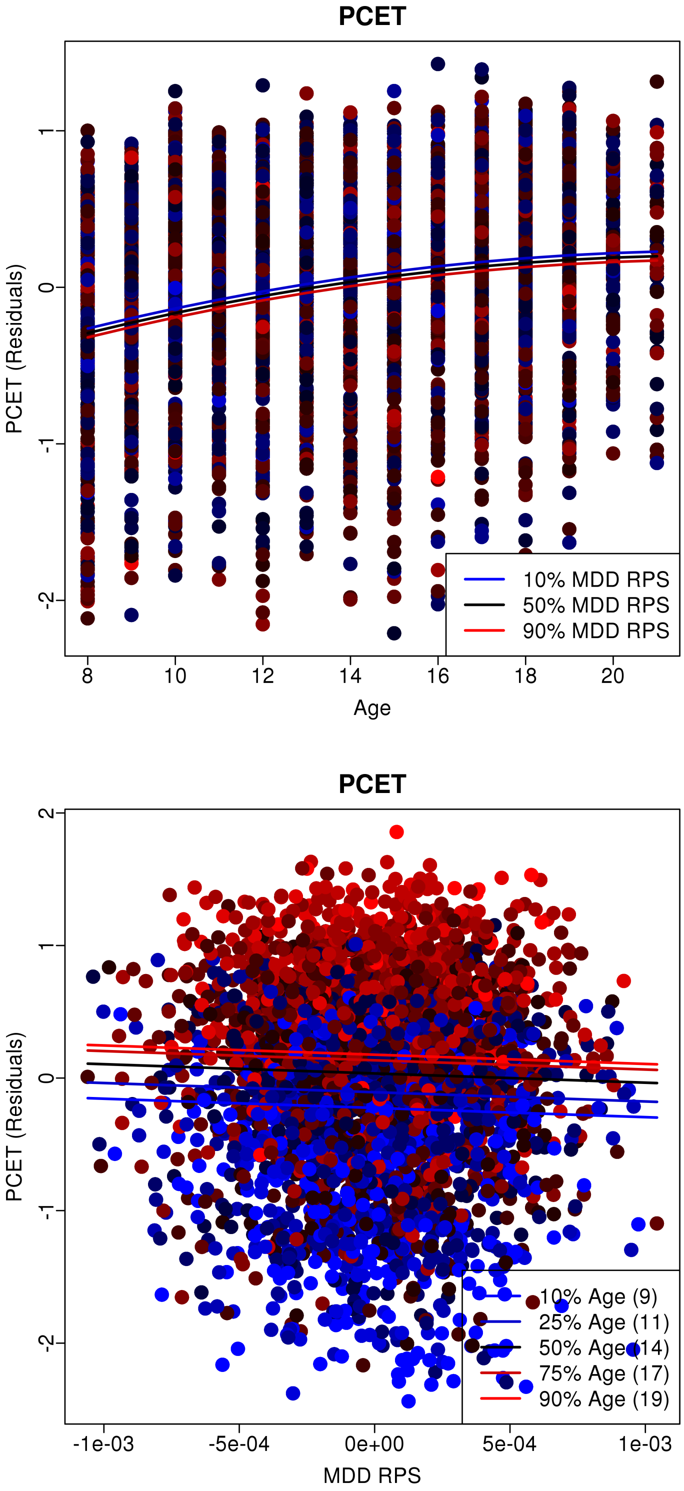
Supporting Figure 5: Correlation among 5 psychiatric RPS in the PING Study. Bipolar Disorder (BIP), Schizophrenia (SCZ), Attention Deficit-Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Major Depressive Disorder (MDD).



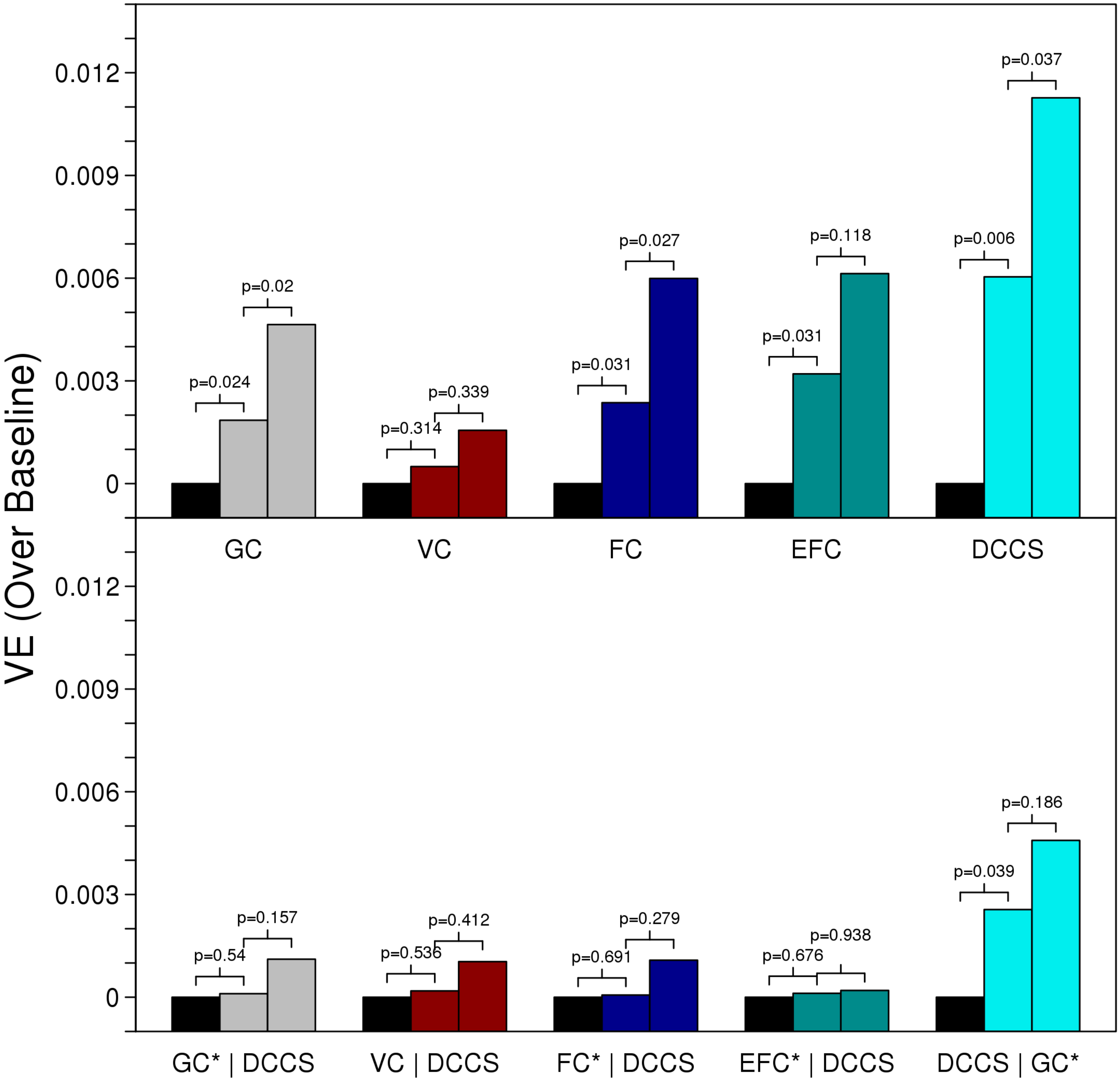
Supporting Figure 6: Visualized RPS effect: ASD-DCCS. The top panel plots the residuals of our model with the effects of age, age^2, RPS, RPSxAge, and RPSxAge^2 added back in (y-axis) against age (x-axis). Curves show expected age trajectories for 10th, 50th and 90th percentile of the RPS. Data points are color coded according to the observed RPS. The bottom panel plot the same residuals (y-axis) against RPS (x-axis) and projects various ages across the RPS range.



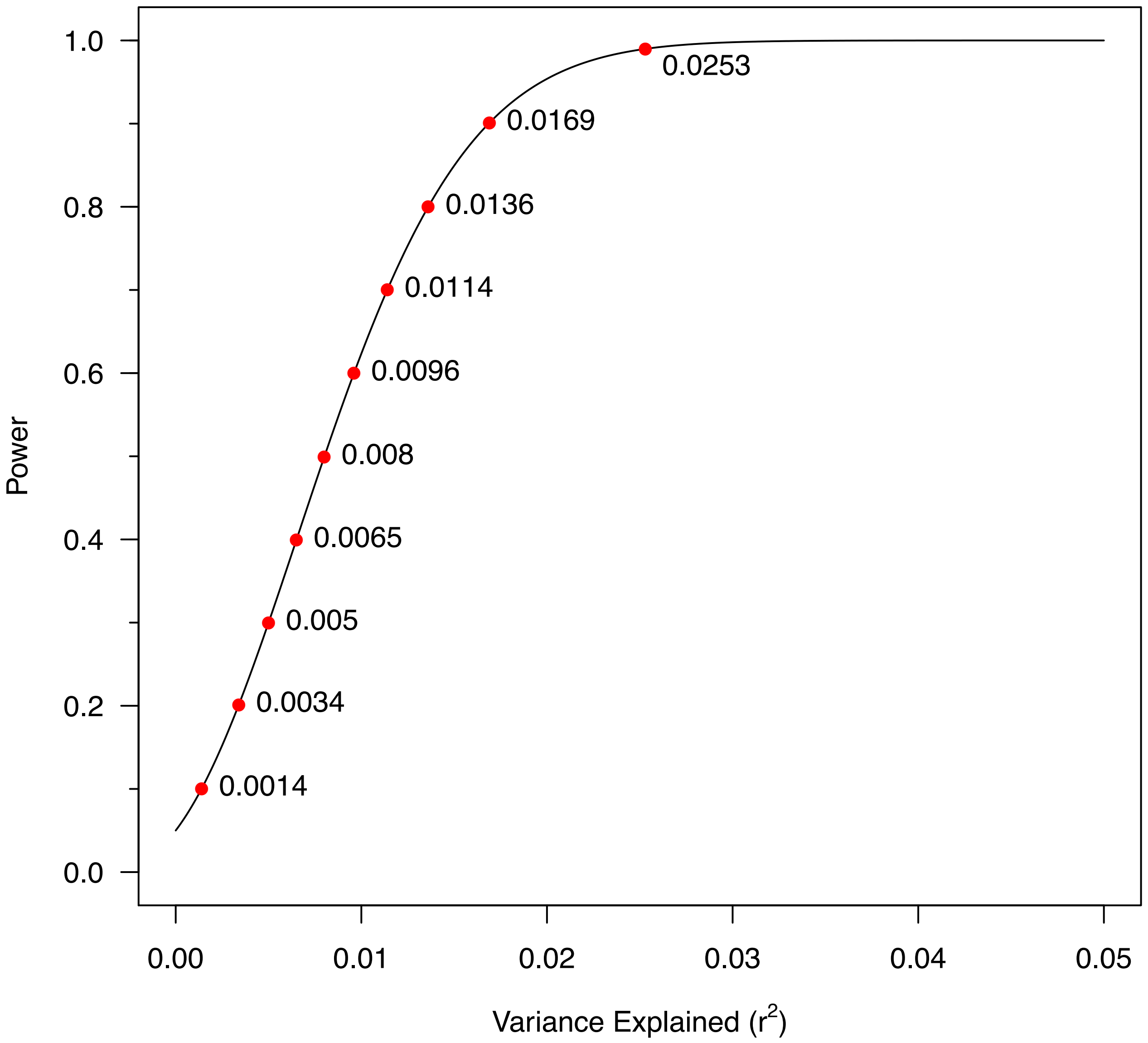
Supporting Figure 7. Visualized RPS effect: MDD-Flanker. The top panel plots the residuals of our model with the effects of age, age^2, RPS, RPSxAge, and RPSxAge^2 added back in (y-axis) against age (x-axis). Curves show expected age trajectories for 10th, 50th and 90th percentile of the RPS. Data points are color coded according to the observed RPS. The bottom panel plot the same residuals (y-axis) against RPS (x-axis) and projects various ages across the RPS range.



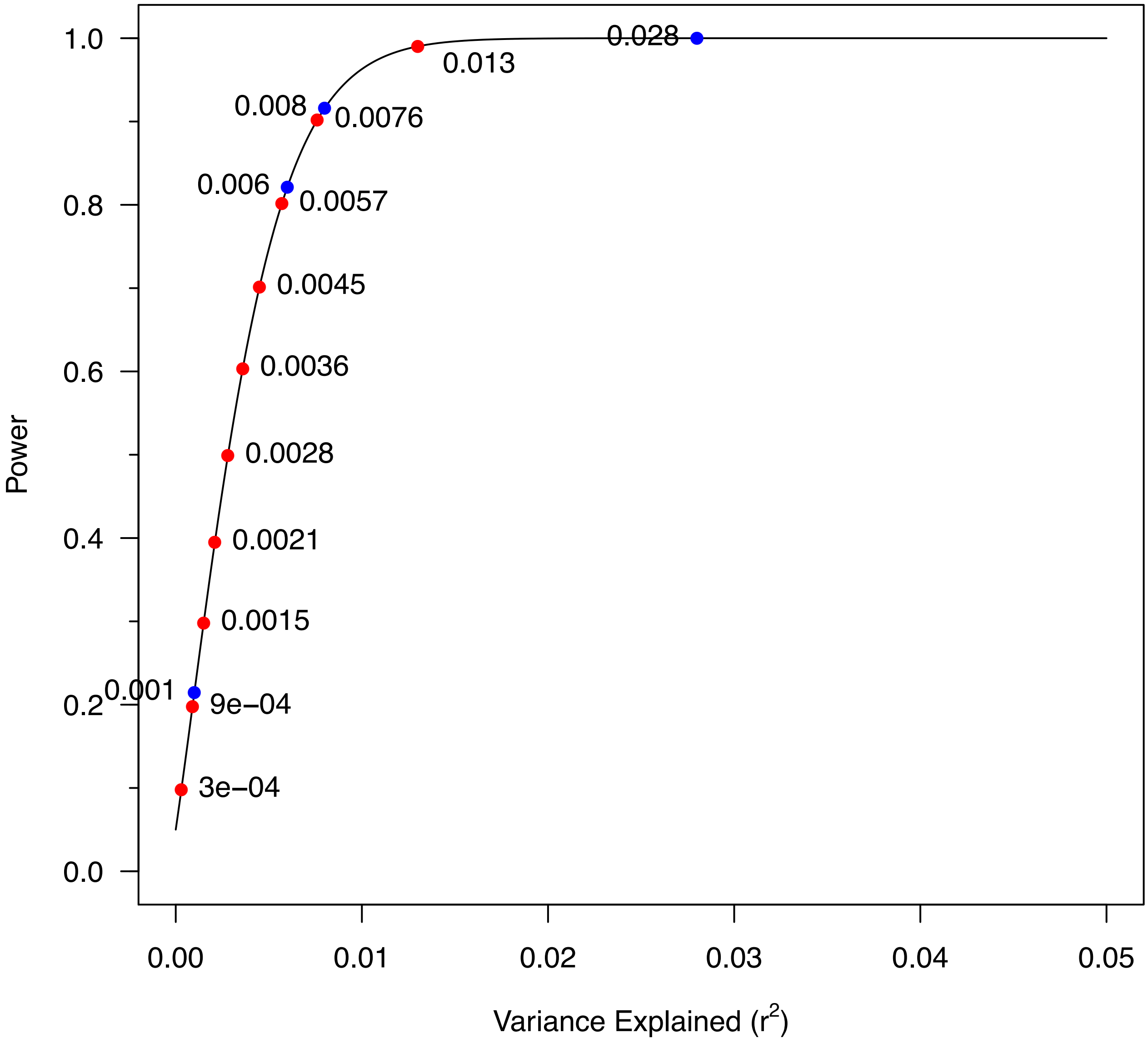
Supporting Figure 8. Visualized RPS effect: MDD-PCET. The top panel plots the residuals of our model with the effects of age, age^2, RPS, RPSxAge, and RPSxAge^2 added back in (y-axis) against age (x-axis). Curves show expected age trajectories for 10th, 50th and 90th percentile of the RPS. Data points are color coded according to the observed RPS. The bottom panel plot the same residuals (y-axis) against RPS (x-axis) and projects various ages across the RPS range.



Supporting Figure 9. Replication of ASD-GC and Comparison with ASD-DCCS. The top panel shows the variance explained in four composite measures, general cognitive (GC), verbal composite (VC), fluid/performance composite (FC), and executive composite (EFC), as well as for the DCCS test alone. For all of the domains that include the DCCS, there is a nominally significant association ($p<0.05$), including for the GC. The bottom panel excludes the DCCS from the computation of each composite (denoted by the *) and includes it instead as a baseline covariate. This essentially removed the RPS effect on the composite. For the DCCS, the GC that did not include DCCS (GC*) is used as a covariate and shows while the effect is slightly reduced, it remains significant.



Supporting Figure 10. Power of the omnibus test to detect aggregate effects in the PING discovery sample. Here we present the power curve to detect aggregate PRS and PRS x Age effects explaining various proportions of variance at $p < 0.05$ in our discovery sample of 417 individuals. The details on the power analysis are presented in above in the section “Supporting Note: Power Analysis.” Red dots mark deciles of power and the labels present the variance explained corresponding to each decile of power.



Supporting Figure 11. Power to detect single PRS effects in the PING discovery sample. Here we present the power curve to detect a single PRS explaining various proportions of variance at $p < 0.05$ in our discovery sample of 417 individuals. The details on the power analysis are presented in above in the section "Supporting Note: Power Analysis." Blue dots represent to the variance explained by the ADHD, MDD, ASD and BIP PRS from within disorder out of sample tests presented in Table 1. Red dots mark deciles of power and the labels present the variance explained corresponding to each decile of power.

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.6408	0.2141	-2.99	0.0029
Age	0.3457	0.0309	11.18	2.79×10^{-25}
Age^2	-0.0074	0.0012	-6.01	4.48×10^{-9}
Gender (Male)	0.0275	0.0519	0.53	0.5960
Site (Davis)	-0.1166	0.1205	-0.97	0.3336
Site (Hawaii)	0.2162	0.1441	1.50	0.1342
Site (KKI)	0.0698	0.1143	0.61	0.5416
Site (LA)	0.2419	0.1760	1.37	0.1700
Site (MGH)	0.1727	0.1135	1.52	0.1290
Site (UCSD)	0.0143	0.1066	0.13	0.8934
Site (UMMS)	-0.0195	0.1308	-0.15	0.8813
Site (Yale)	0.0414	0.1222	0.34	0.7352
Household Income	0.0296	0.0138	2.14	0.0327
Highest Education	0.0568	0.0324	1.75	0.0805
PC1	1.1927	0.7024	1.70	0.0904
PC2	-0.6830	0.6154	-1.11	0.2678
PC3	1.0086	0.5727	1.76	0.0790
PC4	1.4537	0.6644	2.19	0.0293
PC5	0.6136	0.6529	0.94	0.3479
PC6	0.3668	0.6157	0.60	0.5516
PC7	-0.6577	0.5816	-1.13	0.2588
PC8	-1.1522	0.6080	-1.90	0.0588
PC9	0.2591	0.6261	0.41	0.6792
PC10	0.8166	0.6400	1.28	0.2028
ADHD	0.0002	0.0006	0.36	0.7181
ASD	0.0269	0.0107	2.53	0.0120
BIP	0.0122	0.0173	0.70	0.4825
MDD	-0.0429	0.0167	-2.57	0.0106
SCZ2	-0.0185	0.0180	-1.02	0.3063
Age x ADHD	0.0004	0.0006	0.70	0.4873
Age x ASD	0.0210	0.0119	1.77	0.0782
Age x BIP	-0.0093	0.0195	-0.48	0.6342
Age x MDD	0.0042	0.0187	0.23	0.8207
Age x SCZ2	-0.0222	0.0201	-1.10	0.2710
Age^2 x ADHD	-1.61×10^{-5}	2.62×10^{-5}	-0.61	0.5402
Age^2 x ASD	-0.0009	0.0005	-1.86	0.0640
Age^2 x BIP	0.0003	0.0008	0.35	0.7257
Age^2 x MDD	-0.0005	0.0008	-0.72	0.4726
Age^2 x SCZ2	0.0012	0.0008	1.51	0.1320

Supporting Table 1: Primary Test, Full Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.5270	0.2386	-2.21	0.0278
Age	0.3124	0.0344	9.07	5.9 x 10^{-18}
Age^2	-0.0058	0.0014	-4.23	3.0 x 10^{-5}
Gender (Male)	-0.0879	0.0580	-1.52	0.1301
Site (Davis)	-0.1190	0.1361	-0.87	0.3824
Site (Hawaii)	0.0999	0.1624	0.62	0.5388
Site (KKI)	-0.0938	0.1279	-0.73	0.4636
Site (LA)	0.1855	0.1979	0.94	0.3492
Site (MGH)	0.2036	0.1273	1.60	0.1105
Site (UCSD)	-0.0568	0.1201	-0.47	0.6367
Site (UMMS)	-0.0199	0.1470	-0.14	0.8926
Site (Yale)	-0.0159	0.1375	-0.12	0.9081
Household Income	0.0227	0.0152	1.50	0.1349
Highest Education	0.0659	0.0357	1.84	0.0659
PC1	1.0327	0.7672	1.35	0.1790
PC2	-0.8433	0.6772	-1.25	0.2138
PC3	1.2396	0.6441	1.92	0.0550
PC4	1.5884	0.7473	2.13	0.0342
PC5	0.7708	0.7096	1.09	0.2780
PC6	0.2258	0.6900	0.33	0.7437
PC7	-0.4411	0.6436	-0.69	0.4934
PC8	-1.1768	0.6834	-1.72	0.0859
PC9	0.1092	0.7018	0.16	0.8764
PC10	0.8062	0.7213	1.12	0.2644
ASD	0.0324	0.0119	2.72	0.0068
Age x ASD	0.0301	0.0132	2.29	0.0227
Age^2 x ASD	-0.0013	0.0005	-2.47	0.0138

Supporting Table 2: ASD-DCCS without VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.4596	0.2419	-1.90	0.0581
Age	0.3108	0.0349	8.91	1.94×10^{-17}
Age^2	-0.0057	0.0014	-4.13	4.47×10^{-5}
Gender (Male)	-0.0922	0.0587	-1.57	0.1170
Site (Davis)	-0.1332	0.1374	-0.97	0.3331
Site (Hawaii)	0.0579	0.1634	0.35	0.7233
Site (KKI)	-0.0943	0.1295	-0.73	0.4670
Site (LA)	0.2104	0.2009	1.05	0.2956
Site (MGH)	0.1705	0.1286	1.33	0.1856
Site (UCSD)	-0.0729	0.1216	-0.60	0.5492
Site (UMMS)	-0.0358	0.1489	-0.24	0.8102
Site (Yale)	-0.0340	0.1395	-0.24	0.8079
Household Income	0.0265	0.0154	1.73	0.0849
Highest Education	0.0531	0.0364	1.46	0.1454
PC1	0.8579	0.7742	1.11	0.2685
PC2	-0.8203	0.6837	-1.20	0.2309
PC3	1.2766	0.6524	1.96	0.0511
PC4	1.6338	0.7532	2.17	0.0307
PC5	0.7332	0.7188	1.02	0.3083
PC6	0.2842	0.6971	0.41	0.6837
PC7	-0.5074	0.6524	-0.78	0.4372
PC8	-1.0944	0.6945	-1.58	0.1159
PC9	0.0020	0.7084	0.00	0.9978
PC10	0.9024	0.7303	1.24	0.2174
MDD	-0.0236	0.0190	-1.25	0.2131

Supporting Table 3: MDD-DCCS without VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.3855	0.2422	-1.59	0.1122
AgeNP	0.2474	0.0416	5.95	5.84×10^{-9}
AgeNP^2	-0.0045	0.0014	-3.12	0.0019
Gender (Male)	-0.1069	0.0579	-1.85	0.0656
Site (Davis)	-0.1363	0.1351	-1.01	0.3137
Site (Hawaii)	0.1276	0.1613	0.79	0.4296
Site (KKI)	-0.0905	0.1269	-0.71	0.4760
Site (LA)	0.1660	0.1964	0.85	0.3986
Site (MGH)	0.1787	0.1266	1.41	0.1587
Site (UCSD)	-0.0677	0.1192	-0.57	0.5702
Site (UMMS)	-0.0396	0.1460	-0.27	0.7864
Site (Yale)	-0.0300	0.1365	-0.22	0.8264
Household Income	0.0192	0.0151	1.27	0.2054
Highest Education	0.0506	0.0359	1.41	0.1591
PC1	0.9191	0.7620	1.21	0.2285
PC2	-1.0239	0.6748	-1.52	0.1300
PC3	1.1228	0.6402	1.75	0.0802
PC4	1.5192	0.7416	2.05	0.0412
PC5	0.8531	0.7044	1.21	0.2266
PC6	0.1349	0.6851	0.20	0.8440
PC7	-0.4074	0.6383	-0.64	0.5237
PC8	-1.1502	0.6779	-1.70	0.0905
PC9	0.0215	0.6968	0.03	0.9753
PC10	0.5818	0.7200	0.81	0.4195
CC	0.1812	0.0660	2.74	0.0063
ASD	0.0308	0.0118	2.60	0.0098
Age x ASD	0.0278	0.0131	2.13	0.0340
Age^2 x ASD	-0.0012	0.0005	-2.34	0.0198

Supporting Table 4: ASD-DCCS with VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.3151	0.2448	-1.29	0.1987
Age	0.2416	0.0420	5.75	1.83×10^{-8}
Age^2	-0.0043	0.0015	-2.98	0.0030
Gender (Male)	-0.1115	0.0585	-1.91	0.0575
Site (Davis)	-0.1500	0.1363	-1.10	0.2716
Site (Hawaii)	0.0869	0.1622	0.54	0.5925
Site (KKI)	-0.0909	0.1283	-0.71	0.4788
Site (LA)	0.1884	0.1992	0.95	0.3449
Site (MGH)	0.1461	0.1276	1.14	0.2530
Site (UCSD)	-0.0840	0.1205	-0.70	0.4861
Site (UMMS)	-0.0558	0.1477	-0.38	0.7058
Site (Yale)	-0.0479	0.1383	-0.35	0.7292
Household Income	0.0227	0.0153	1.49	0.1377
Highest Education	0.0376	0.0364	1.03	0.3030
PC1	0.7405	0.7681	0.96	0.3356
PC2	-1.0021	0.6802	-1.47	0.1415
PC3	1.1548	0.6477	1.78	0.0754
PC4	1.5442	0.7469	2.07	0.0393
PC5	0.8260	0.7128	1.16	0.2473
PC6	0.1904	0.6914	0.28	0.7831
PC7	-0.4691	0.6465	-0.73	0.4685
PC8	-1.0762	0.6880	-1.56	0.1186
PC9	-0.0780	0.7023	-0.11	0.9117
PC10	0.6644	0.7282	0.91	0.3621
CC	0.1929	0.0666	2.89	0.0040
MDD	-0.0217	0.0188	-1.15	0.2490

Supporting Table 5: MDD-DCCS with VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.6602	0.2499	-2.64	0.0086
Age	0.3617	0.0361	10.03	3.36×10^{-21}
Age^2	-0.0081	0.0014	-5.69	2.46×10^{-8}
Gender (Male)	0.1084	0.0607	1.79	0.0749
Site (Davis)	-0.1727	0.1425	-1.21	0.2263
Site (Hawaii)	0.2478	0.1701	1.46	0.1459
Site (KKI)	0.0968	0.1340	0.72	0.4703
Site (LA)	0.1937	0.2073	0.93	0.3506
Site (MGH)	0.0396	0.1333	0.30	0.7666
Site (UCSD)	0.0007	0.1258	0.01	0.9953
Site (UMMS)	-0.1373	0.1540	-0.89	0.3730
Site (Yale)	0.0753	0.1440	0.52	0.6015
Household Income	0.0276	0.0159	1.74	0.0833
Highest Education	0.0608	0.0374	1.62	0.1050
PC1	0.3714	0.8036	0.46	0.6442
PC2	-0.8383	0.7094	-1.18	0.2380
PC3	0.9407	0.6747	1.39	0.1640
PC4	1.4466	0.7828	1.85	0.0653
PC5	1.1571	0.7433	1.56	0.1203
PC6	0.3711	0.7227	0.51	0.6079
PC7	-0.9556	0.6741	-1.42	0.1571
PC8	-1.2565	0.7159	-1.76	0.0800
PC9	0.3990	0.7351	0.54	0.5876
PC10	0.4681	0.7555	0.62	0.5359
ASD	0.0126	0.0125	1.01	0.3128
Age x ASD	0.0140	0.0138	1.01	0.3123
Age^2 x ASD	-0.0006	0.0006	-1.05	0.2926

Supporting Table 6: ASD-Flanker without VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.5891	0.2476	-2.38	0.0178
Age	0.3582	0.0357	10.03	3.10×10^{-21}
Age^2	-0.0080	0.0014	-5.68	2.60×10^{-8}
Gender (Male)	0.0995	0.0601	1.66	0.0984
Site (Davis)	-0.1899	0.1407	-1.35	0.1777
Site (Hawaii)	0.2339	0.1673	1.40	0.1628
Site (KKI)	0.1047	0.1325	0.79	0.4298
Site (LA)	0.2310	0.2057	1.12	0.2621
Site (MGH)	0.0387	0.1316	0.29	0.7690
Site (UCSD)	-0.0035	0.1245	-0.03	0.9777
Site (UMMS)	-0.1406	0.1524	-0.92	0.3569
Site (Yale)	0.0496	0.1428	0.35	0.7285
Household Income	0.0315	0.0157	2.00	0.0460
Highest Education	0.0460	0.0372	1.24	0.2173
PC1	0.4272	0.7925	0.54	0.5901
PC2	-0.7431	0.6998	-1.06	0.2889
PC3	1.0306	0.6678	1.54	0.1236
PC4	1.4293	0.7710	1.85	0.0645
PC5	1.1886	0.7357	1.62	0.1070
PC6	0.4467	0.7135	0.63	0.5316
PC7	-0.9093	0.6677	-1.36	0.1740
PC8	-1.0903	0.7108	-1.53	0.1259
PC9	0.4415	0.7251	0.61	0.5429
PC10	0.5610	0.7475	0.75	0.4534
MDD	-0.0542	0.0194	-2.79	0.0055

Supporting Table 7: MDD-Flanker without VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.6050	0.2558	-2.37	0.0185
Age	0.3364	0.0439	7.66	1.45×10^{-13}
Age^2	-0.0076	0.0015	-5.04	7.04×10^{-7}
Gender (Male)	0.1010	0.0612	1.65	0.0994
Site (Davis)	-0.1794	0.1427	-1.26	0.2092
Site (Hawaii)	0.2586	0.1704	1.52	0.1299
Site (KKI)	0.0981	0.1340	0.73	0.4644
Site (LA)	0.1861	0.2075	0.90	0.3702
Site (MGH)	0.0299	0.1337	0.22	0.8230
Site (UCSD)	-0.0035	0.1258	-0.03	0.9777
Site (UMMS)	-0.1450	0.1542	-0.94	0.3475
Site (Yale)	0.0698	0.1441	0.48	0.6284
Household Income	0.0262	0.0160	1.64	0.1012
Highest Education	0.0549	0.0379	1.45	0.1484
PC1	0.3271	0.8047	0.41	0.6846
PC2	-0.9087	0.7127	-1.27	0.2031
PC3	0.8951	0.6761	1.32	0.1863
PC4	1.4196	0.7832	1.81	0.0707
PC5	1.1892	0.7439	1.60	0.1107
PC6	0.3357	0.7235	0.46	0.6430
PC7	-0.9424	0.6742	-1.40	0.1629
PC8	-1.2462	0.7159	-1.74	0.0825
PC9	0.3648	0.7359	0.50	0.6203
PC10	0.3807	0.7604	0.50	0.6169
CC	0.0706	0.0697	1.01	0.3117
ASD	0.0120	0.0125	0.96	0.3391
Age x ASD	0.0131	0.0138	0.95	0.3450
Age^2 x ASD	-0.0006	0.0006	-1.00	0.3193

Supporting Table 8: ASD-Flanker with VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.5363	0.2529	-2.12	0.0345
Age	0.3329	0.0434	7.67	1.41×10^{-13}
Age^2	-0.0075	0.0015	-5.03	7.55×10^{-7}
Gender (Male)	0.0925	0.0605	1.53	0.1270
Site (Davis)	-0.1961	0.1408	-1.39	0.1644
Site (Hawaii)	0.2445	0.1676	1.46	0.1454
Site (KKI)	0.1060	0.1325	0.80	0.4244
Site (LA)	0.2229	0.2058	1.08	0.2794
Site (MGH)	0.0298	0.1319	0.23	0.8215
Site (UCSD)	-0.0076	0.1245	-0.06	0.9516
Site (UMMS)	-0.1479	0.1526	-0.97	0.3329
Site (Yale)	0.0445	0.1429	0.31	0.7556
Household Income	0.0301	0.0158	1.91	0.0573
Highest Education	0.0403	0.0376	1.07	0.2844
PC1	0.3843	0.7935	0.48	0.6284
PC2	-0.8095	0.7027	-1.15	0.2500
PC3	0.9861	0.6692	1.47	0.1414
PC4	1.3965	0.7716	1.81	0.0711
PC5	1.2225	0.7364	1.66	0.0977
PC6	0.4125	0.7143	0.58	0.5640
PC7	-0.8953	0.6678	-1.34	0.1808
PC8	-1.0837	0.7108	-1.52	0.1282
PC9	0.4123	0.7256	0.57	0.5702
PC10	0.4740	0.7523	0.63	0.5290
CC	0.0705	0.0688	1.02	0.3064
MDD	-0.0535	0.0194	-2.76	0.0061

Supporting Table 9: MDD-Flanker with VC Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	2.0565	0.0292	70.48	0.000
Age	0.1343	0.0243	5.52	3.68×10^{-8}
Age^2	-0.0035	0.0009	-3.95	0.0001
Sex (Male)	0.0718	0.0214	3.36	0.0008
c1	-0.6130	0.6904	-0.89	0.3747
c2	-0.8725	0.6958	-1.25	0.2100
c3	0.6986	0.6979	1.00	0.3169
c4	-0.6569	0.6982	-0.94	0.3468
c5	1.0294	0.6963	1.48	0.1394
c6	0.4345	0.6979	0.62	0.5336
c7	-0.9557	0.7042	-1.36	0.1748
c8	1.4591	0.6933	2.10	0.0354
c9	-0.7383	0.6990	-1.06	0.2909
c10	-0.3537	0.7001	-0.51	0.6135
Medical Rating = 1	0.0031	0.0341	0.09	0.9274
Medical Rating = 2	-0.0395	0.0333	-1.19	0.2349
Medical Rating = 3	-0.0843	0.0362	-2.33	0.0200
Medical Rating = 4	-0.0892	0.0515	-1.73	0.0834
ASD	-0.0254	27.1385	0.00	0.9993
Age x ASD	39.7396	62.1200	0.64	0.5224
Age^2 x ASD	-1.4234	2.2399	-0.64	0.5252

Supporting Table 10: ASD-PCET without WRAT Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	2.0559	0.0291	70.55	0.0000
Age	0.1336	0.0243	5.50	4.07×10^{-8}
Age^2	-0.0034	0.0009	-3.93	8.52×10^{-5}
Sex (Male)	0.0721	0.0214	3.38	0.0007
c1	-0.7226	0.6913	-1.05	0.2960
c2	-0.9057	0.6946	-1.30	0.1923
c3	0.6883	0.6932	0.99	0.3208
c4	-0.6057	0.6978	-0.87	0.3855
c5	0.9405	0.6967	1.35	0.1771
c6	0.4394	0.6970	0.63	0.5285
c7	-0.9415	0.7027	-1.34	0.1804
c8	1.5073	0.6924	2.18	0.0295
c9	-0.7035	0.6979	-1.01	0.3135
c10	-0.4370	0.7002	-0.62	0.5326
Medical Rating = 1	0.0037	0.0340	0.11	0.9144
Medical Rating = 2	-0.0381	0.0333	-1.14	0.2525
Medical Rating = 3	-0.0843	0.0362	-2.33	0.0200
Medical Rating = 4	-0.0882	0.0515	-1.71	0.0866
MDD	-74.1529	33.3097	-2.23	0.0261

Supporting Table 11: MDD-PCET without WRAT Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	1.2578	0.0828	15.19	1.34×10^{-50}
Age	0.1076	0.0241	4.46	8.44×10^{-6}
Age^2	-0.0024	0.0009	-2.77	0.0056
Sex (Male)	0.0599	0.0211	2.83	0.0046
c1	0.2649	0.6860	0.39	0.6994
c2	-0.4811	0.6871	-0.70	0.4839
c3	0.5865	0.6882	0.85	0.3942
c4	-0.8203	0.6886	-1.19	0.2336
c5	1.0219	0.6865	1.49	0.1367
c6	0.4113	0.6881	0.60	0.5501
c7	-0.9501	0.6943	-1.37	0.1712
c8	1.5614	0.6837	2.28	0.0224
c9	-0.8466	0.6892	-1.23	0.2194
c10	-0.4214	0.6903	-0.61	0.5416
Medical Rating = 1	0.0100	0.0336	0.30	0.7659
Medical Rating = 2	-0.0283	0.0328	-0.86	0.3891
Medical Rating = 3	-0.0586	0.0358	-1.64	0.1020
Medical Rating = 4	-0.0545	0.0509	-1.07	0.2847
wrat_cr_std	0.0074	0.0007	10.29	0.0000
ASD	-6.8444	26.7661	-0.26	0.7982
Age x ASD	41.9116	61.2490	0.68	0.4938
Age^2 x ASD	-1.4667	2.2085	-0.66	0.5066

Supporting Table 12: ASD-PCET with WRAT Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	1.2603	0.0827	15.24	6.79×10^{-51}
Age	0.1068	0.0241	4.43	9.61×10^{-6}
Age^2	-0.0024	0.0009	-2.74	0.0061
Sex (Male)	0.0602	0.0211	2.85	0.0043
c1	0.1589	0.6871	0.23	0.8171
c2	-0.5043	0.6860	-0.74	0.4623
c3	0.5975	0.6836	0.87	0.3821
c4	-0.7749	0.6883	-1.13	0.2603
c5	0.9418	0.6870	1.37	0.1705
c6	0.4189	0.6873	0.61	0.5422
c7	-0.9284	0.6929	-1.34	0.1804
c8	1.6057	0.6828	2.35	0.0187
c9	-0.8178	0.6882	-1.19	0.2348
c10	-0.4969	0.6905	-0.72	0.4718
Medical Rating = 1	0.0105	0.0336	0.31	0.7546
Medical Rating = 2	-0.0269	0.0328	-0.82	0.4130
Medical Rating = 3	-0.0585	0.0358	-1.64	0.1021
Medical Rating = 4	-0.0537	0.0509	-1.05	0.2917
wrat_cr_std	0.0074	0.0007	10.26	2.25×10^{-24}
MDD	-69.6343	32.8481	-2.12	0.0341

Supporting Table 13: MDD-PCET with WRAT Model Statistics

	Beta	**S.E.**	**t**	**P**
(Intercept)	-6.32E-01	2.12E-01	-2.984	0.00303
Age	3.55E-01	3.07E-02	11.541	$< 2.00 \times 10^{-16}$
Age^2	-7.71E-03	1.22E-03	-6.297	8.49×10^{-10}
Gender (Male)	2.95E-02	5.14E-02	0.575	0.56575
Site (Davis)	-1.09E-01	1.19E-01	-0.916	0.36043
Site (Hawaii)	2.52E-01	1.43E-01	1.76	0.07916
Site (KKI)	9.67E-02	1.13E-01	0.853	0.3941
Site (LA)	2.46E-01	1.74E-01	1.41	0.15936
Site (MGH)	2.32E-01	1.14E-01	2.039	0.04213
Site (UCSD)	4.64E-02	1.06E-01	0.438	0.66173
Site (UMMS)	-7.07E-03	1.30E-01	-0.055	0.95651
Site (Yale)	6.63E-02	1.21E-01	0.547	0.58476
Household Income	2.70E-02	1.37E-02	1.975	0.04901
Highest Education	5.91E-02	3.21E-02	1.842	0.06631
PC1	1.30E+00	6.96E-01	1.869	0.06234
PC2	-5.98E-01	6.09E-01	-0.982	0.32694
PC3	9.39E-01	5.67E-01	1.655	0.09883
PC4	1.34E+00	6.58E-01	2.035	0.04257
PC5	7.65E-01	6.48E-01	1.181	0.23832
PC6	2.35E-01	6.11E-01	0.384	0.70102
PC7	-5.60E-01	5.76E-01	-0.972	0.33187
PC8	-1.07E+00	6.02E-01	-1.773	0.07698
PC9	3.03E-01	6.19E-01	0.489	0.62495
PC10	7.40E-01	6.36E-01	1.164	0.2451
Dx_ADHD	-2.28E-01	9.58E-02	-2.385	0.0176
Dx_LearnDis	-1.38E-01	1.09E-01	-1.262	0.20772
ADHD	1.39E-04	5.82E-04	0.239	0.81133
ASD	2.83E-02	1.06E-02	2.681	0.00766
BIP	9.22E-03	1.71E-02	0.538	0.59107
MDD	-4.28E-02	1.65E-02	-2.593	0.00989
SCZ2	-2.09E-02	1.79E-02	-1.171	0.24222
Age x ADHD	3.21E-04	6.30E-04	0.509	0.61123
Age x ASD	1.90E-02	1.18E-02	1.617	0.10679
Age x BIP	-6.17E-03	1.94E-02	-0.319	0.75002
Age x MDD	4.97E-03	1.85E-02	0.268	0.78878
Age x SCZ2	-2.34E-02	2.00E-02	-1.17	0.24261
Age^2 x ADHD	-1.03E-05	2.60E-05	-0.398	0.69079
Age^2 x ASD	-8.04E-04	4.76E-04	-1.69	0.09187
Age^2 x BIP	1.83E-04	7.83E-04	0.233	0.81565
Age^2 x MDD	-5.71E-04	7.48E-04	-0.763	0.44594
Age^2 x SCZ2	1.24E-03	7.74E-04	1.603	0.10986

Supporting Table 14: Full Primary Test Model Statistics, including diagnosis variables

	Beta	**S.E.**	**t**	**P**
(Intercept)	-6.94E-01	2.28E-01	-3.047	0.0025
Age	3.54E-01	3.29E-02	10.743	$< 2 \times 10^{-16}$
Age^2	-7.59E-03	1.32E-03	-5.751	2.04×10^{-08}
Gender (Male)	8.25E-03	5.54E-02	0.149	0.8816
Site (Davis)	-1.00E-01	1.25E-01	-0.802	0.4229
Site (Hawaii)	2.17E-01	1.55E-01	1.399	0.1627
Site (KKI)	8.34E-02	1.20E-01	0.696	0.487
Site (LA)	2.28E-01	1.78E-01	1.279	0.202
Site (MGH)	2.06E-01	1.23E-01	1.67	0.0959
Site (UCSD)	3.04E-02	1.11E-01	0.275	0.7838
Site (UMMS)	-7.12E-03	1.36E-01	-0.052	0.9583
Site (Yale)	4.87E-02	1.26E-01	0.387	0.6988
Household Income	3.73E-02	1.53E-02	2.445	0.015
Highest Education	5.97E-02	3.49E-02	1.71	0.0882
PC1	1.14E+00	7.57E-01	1.508	0.1326
PC2	-8.19E-01	6.38E-01	-1.284	0.2
PC3	9.56E-01	5.89E-01	1.624	0.1054
PC4	1.37E+00	6.88E-01	1.985	0.048
PC5	7.60E-01	6.80E-01	1.117	0.2646
PC6	3.31E-01	6.53E-01	0.507	0.6126
PC7	-5.20E-01	6.03E-01	-0.861	0.3897
PC8	-9.20E-01	6.25E-01	-1.471	0.1422
PC9	1.41E-01	6.46E-01	0.218	0.8277
PC10	8.95E-01	6.64E-01	1.348	0.1785
ADHD	-1.51E-05	6.18E-04	-0.024	0.9805
ASD	2.54E-02	1.16E-02	2.182	0.0298
BIP	9.46E-03	1.86E-02	0.508	0.6118
MDD	-4.69E-02	1.83E-02	-2.567	0.0107
SCZ2	-1.03E-02	1.94E-02	-0.531	0.5955
Age x ADHD	3.41E-04	6.56E-04	0.519	0.6041
Age x ASD	1.14E-02	1.29E-02	0.882	0.3785
Age x BIP	-1.87E-02	2.09E-02	-0.896	0.3711
Age x MDD	1.35E-02	2.02E-02	0.669	0.5042
Age x SCZ2	-2.49E-02	2.22E-02	-1.123	0.2621
Age^2 x ADHD	-1.21E-05	2.71E-05	-0.448	0.6543
Age^2 x ASD	-4.81E-04	5.20E-04	-0.925	0.3557
Age^2 x BIP	6.96E-04	8.46E-04	0.822	0.4116
Age^2 x MDD	-9.20E-04	8.26E-04	-1.114	0.2661
Age^2 x SCZ2	1.24E-03	8.69E-04	1.427	0.1546

Supporting Table 15: Full Primary Test Model Statistics, Censoring Diagnoses Individuals

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.5079106	0.2360347	-2.152	0.03203
Age	0.3245949	0.0342601	9.474	< 2.00E-16
Age^2	-0.006223	0.0013574	-4.584	6.15E-06
Gender (Male)	-0.0863932	0.0573607	-1.506	0.13284
Site (Davis)	-0.1141955	0.1346391	-0.848	0.39687
Site (Hawaii)	0.1412482	0.161043	0.877	0.38098
Site (KKI)	-0.0588996	0.1269374	-0.464	0.6429
Site (LA)	0.1788296	0.1957516	0.914	0.36152
Site (MGH)	0.2646386	0.1272532	2.08	0.03822
Site (UCSD)	-0.0214738	0.1192337	-0.18	0.85717
Site (UMMS)	-0.0129856	0.1456672	-0.089	0.92901
Site (Yale)	0.0016668	0.136162	0.012	0.99024
Household Income	0.019815	0.015044	1.317	0.18857
Highest Education	0.0673182	0.0353447	1.905	0.05757
PC1	1.1237015	0.7591607	1.48	0.13963
PC2	-0.7110106	0.6713016	-1.059	0.29019
PC3	1.1559833	0.6376891	1.813	0.07064
PC4	1.457675	0.7404448	1.969	0.0497
PC5	0.9463256	0.7042941	1.344	0.17985
PC6	0.0805828	0.6837328	0.118	0.90624
PC7	-0.3792536	0.6366667	-0.596	0.55173
PC8	-1.0973647	0.6763712	-1.622	0.10552
PC9	0.1829575	0.6944113	0.263	0.79233
PC10	0.6562405	0.7155536	0.917	0.35966
Dx_ADHD	-0.1618092	0.1075495	-1.505	0.13326
Dx_LearnDis	-0.2792733	0.1233143	-2.265	0.02408
ASD	0.034478	0.0118087	2.92	0.00371
Age x ASD	0.0277903	0.0130437	2.131	0.03375
Age^2 x ASD	-0.0012248	0.0005268	-2.325	0.02059

Supporting Table 16: ASD-DCCS without VC Model Statistics, Including Diagnosis Variables

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.6267111	0.2525489	-2.482	0.0136
Age	0.3189558	0.0363543	8.774	< 2.00E-16
Age^2	-0.0058594	0.0014475	-4.048	6.41E-05
Gender (Male)	-0.0962888	0.0618443	-1.557	0.1204
Site (Davis)	-0.1144122	0.1398837	-0.818	0.414
Site (Hawaii)	0.131226	0.1743132	0.753	0.4521
Site (KKI)	-0.0925512	0.133545	-0.693	0.4888
Site (LA)	0.1731788	0.1990557	0.87	0.3849
Site (MGH)	0.2626021	0.1365375	1.923	0.0553
Site (UCSD)	-0.027176	0.1243205	-0.219	0.8271
Site (UMMS)	-0.0095173	0.1522461	-0.063	0.9502
Site (Yale)	-0.0254137	0.1410208	-0.18	0.8571
Household Income	0.0322661	0.0167003	1.932	0.0542
Highest Education	0.0734983	0.0384639	1.911	0.0569
PC1	0.9972403	0.8199399	1.216	0.2247
PC2	-0.9690806	0.7028563	-1.379	0.1689
PC3	1.1899571	0.6599976	1.803	0.0723
PC4	1.5865577	0.7703587	2.06	0.0402
PC5	0.8835733	0.7282834	1.213	0.2259
PC6	0.1548245	0.7280639	0.213	0.8317
PC7	-0.4265134	0.6623842	-0.644	0.5201
PC8	-1.1295033	0.6984545	-1.617	0.1068
PC9	-0.1381187	0.7229752	-0.191	0.8486
PC10	0.7977075	0.7426881	1.074	0.2836
ASD	0.032367	0.0129515	2.499	0.0129
Age x ASD	0.0240276	0.0141866	1.694	0.0912
Age^2 x ASD	-0.0010623	0.0005714	-1.859	0.0639

Supporting Table 17: ASD-DCCS without VC Model Statistics, Censoring Diagnoses Individuals

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.579392	0.246143	-2.354	0.01907
Age	0.36541	0.03571	10.233	< 2.00E-16
Age^2	-0.008276	0.001415	-5.851	1.04E-08
Gender (Male)	0.103225	0.059746	1.728	0.08483
Site (Davis)	-0.176075	0.139941	-1.258	0.20907
Site (Hawaii)	0.257345	0.166744	1.543	0.12356
Site (KKI)	0.121692	0.132149	0.921	0.35769
Site (LA)	0.229584	0.20444	1.123	0.26213
Site (MGH)	0.082154	0.132289	0.621	0.53495
Site (UCSD)	0.021547	0.124239	0.173	0.8624
Site (UMMS)	-0.120124	0.151831	-0.791	0.42933
Site (Yale)	0.069585	0.142189	0.489	0.62485
Household Income	0.030016	0.01566	1.917	0.05601
Highest Education	0.0465	0.03701	1.256	0.20972
PC1	0.486268	0.788117	0.617	0.53759
PC2	-0.623874	0.697272	-0.895	0.37148
PC3	1.013778	0.664446	1.526	0.12788
PC4	1.311201	0.767838	1.708	0.0885
PC5	1.348746	0.734078	1.837	0.06692
PC6	0.372245	0.710516	0.524	0.60064
PC7	-0.863631	0.66405	-1.301	0.19418
PC8	-1.017217	0.707155	-1.438	0.1511
PC9	0.504229	0.721239	0.699	0.4849
PC10	0.526998	0.745284	0.707	0.47992
Dx_ADHD	-0.27103	0.111693	-2.427	0.01569
Dx_LearnDis	-0.008177	0.128081	-0.064	0.94913
MDD	-0.053965	0.019293	-2.797	0.00541

Supporting Table 18: MDD-Flanker without VC Model Statistics, Including Diagnosis Variables

	Beta	**S.E.**	**t**	**P**
(Intercept)	-0.585243	0.262848	-2.227	0.02663
Age	0.368602	0.037755	9.763	< 2.00E-16
Age^2	-0.008385	0.001503	-5.58	4.91E-08
Gender (Male)	0.075946	0.064313	1.181	0.23848
Site (Davis)	-0.171156	0.145106	-1.18	0.23901
Site (Hawaii)	0.260369	0.179936	1.447	0.14882
Site (KKI)	0.152282	0.138725	1.098	0.2731
Site (LA)	0.227807	0.207768	1.096	0.27366
Site (MGH)	0.065514	0.141843	0.462	0.64446
Site (UCSD)	0.014456	0.129363	0.112	0.91109
Site (UMMS)	-0.138532	0.158542	-0.874	0.38285
Site (Yale)	0.075353	0.147075	0.512	0.60874
Household Income	0.038183	0.017267	2.211	0.02768
Highest Education	0.039811	0.040023	0.995	0.32058
PC1	0.384844	0.849282	0.453	0.65074
PC2	-0.98465	0.72842	-1.352	0.17735
PC3	0.903224	0.685315	1.318	0.1884
PC4	1.259059	0.79834	1.577	0.1157
PC5	1.603197	0.757441	2.117	0.03502
PC6	0.372136	0.752054	0.495	0.62104
PC7	-0.670917	0.689587	-0.973	0.33128
PC8	-0.751432	0.72782	-1.032	0.3026
PC9	0.395331	0.745994	0.53	0.5965
PC10	0.673841	0.77218	0.873	0.38347
MDD	-0.062239	0.021114	-2.948	0.00342

Supporting Table 19: MDD-Flanker without VC Model Statistics, Censoring Diagnosed Individuals