Archival Report

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Examining Differences in the Genetic and Functional Architecture of Attention-Deficit/Hyperactivity Disorder Diagnosed in Childhood and Adulthood

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with diagnostic criteria requiring symptoms to begin in childhood. We investigated whether individuals diagnosed as children differ from those diagnosed in adulthood with respect to shared and unique architecture at the genome-wide and gene expression level of analysis.

METHODS: We used genomic structural equation modeling (SEM) to investigate differences in genetic correlations (r_g) of childhood-diagnosed (n_{cases} = 14,878) and adulthood-diagnosed (n_{cases} = 6961) ADHD with 98 behavioral, psychiatric, cognitive, and health outcomes. We went on to apply transcriptome-wide SEM to identify functional annotations and patterns of gene expression associated with genetic risk sharing or divergence across the ADHD subgroups.

RESULTS: Compared with the childhood subgroup, adulthood-diagnosed ADHD exhibited a significantly larger negative r_g with educational attainment, the noncognitive skills of educational attainment, and age at first sexual intercourse. We observed a larger positive r_g for adulthood-diagnosed ADHD with major depression, suicidal ideation, and a latent internalizing factor. At the gene expression level, transcriptome-wide SEM analyses revealed 22 genes that were significantly associated with shared genetic risk across the subtypes that reflected a mixture of coding and noncoding genes and included 15 novel genes relative to the ADHD subgroups.

CONCLUSIONS: This study demonstrated that ADHD diagnosed later in life shows much stronger genetic overlap with internalizing disorders and related traits. This may indicate the potential clinical relevance of distinguishing these subgroups or increased misdiagnosis for those diagnosed later in life. Top transcriptome-wide SEM results implicated genes related to neuronal function and clinical characteristics (e.g., sleep).

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects approximately 5% of the population and is characterized by a persistent pattern of inattention and/or hyperactivity and impulsivity (1). Although ADHD diagnoses can be given at any age, symptoms must begin before age 12 years to meet diagnostic criteria. Because symptoms should start within the same developmental time frame for everyone, the age at diagnosis theoretically should not reflect a relevant clinical distinction. However, whether ADHD diagnosed later in life is differentially associated with outcomes and predictors remains a largely open question. For a disorder estimated to be approximately 80% heritable (2), genetic tools offer an exciting opportunity to better understand whether age at diagnosis reflects a relevant clinical and etiological specifier.

There are multiple reasons to expect genetic divergence for ADHD diagnosed at different points in development. For example, ADHD diagnosed in childhood may reflect symptoms that are more severe and thereby clinically detectable at a younger age, leading to greater genetic overlap between childhood ADHD and clinical markers of severity (e.g., suicide attempts). Poor retrospective recall of childhood symptoms in adulthood (3) may also result in genetic divergence due to consequent misdiagnosis. Recall bias coupled with shared symptoms between ADHD and other psychiatric disorders may contribute to a higher likelihood of misdiagnosis in adulthood (4). If this misdiagnosis in adulthood were particularly skewed toward one class of disorders, it could result in higher estimates of genetic overlap with these disorders.

The current study applied multivariate genomic tools to examine whether age at ADHD diagnosis demarcates different etiological boundaries and clinical distinctions at multiple levels of biological analysis. At the genome-wide level, we modeled and compared genetic overlap across

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childhood- and adulthood-diagnosed ADHD with psychiatric, cognitive, health, social, and behavioral outcomes. We further examined whether differential gene expression is associated with shared genetic risk or uniqueness across subgroups. These findings collectively offer valuable insight into the shared and unique genetic architecture for ADHD diagnosed early versus later in life.

METHODS AND MATERIALS

Phenotype Selection

ADHD Stratified by Age at Diagnosis. The childhood- and adulthood-diagnosis ADHD genome-wide association studies (GWASs) (hereafter referred to as $ADHD_{child}$ and $ADHD_{adult}$, respectively) were taken from the original article by Rajagopal *et al.* (5), and we conducted a secondary analysis of this dataset, which consists of an ADHD case/control sample from iPSYCH (the Lundbeck Foundation Initiative for Integrative Psychiatric Research). iPSYCH reflects a nationwide population-based sample of individuals born in Denmark between May 1981 and December 2008. ADHD cases reflected individuals in the Danish Psychiatric Central Research Register that were diagnosed by psychiatrists according to ICD-10 criteria (F90.0 diagnosis code) that reflects a disorder that typically displays symptoms by age 5 years. This sample included 14,878 childhood ADHD cases (23% female; mean age = 17.2 years, SD = 4.5), 6961 adulthood ADHD cases (41% female; mean age = 27.8 years, SD = 4.0), and 38,303 controls (49% female; mean age = 22.1 years, SD = 7.3) randomly selected from the same nationwide birth cohort (5). Cases and controls were all European ancestry. Childhood ADHD cases reflected individuals diagnosed before age 18, whereas adulthood ADHD cases consisted of individuals who were diagnosed with ADHD after age 18 and were able to retrospectively recall ADHD symptoms experienced during childhood. The persistent ADHD phenotype (1473 cases), reflecting individuals diagnosed before 18 who continued to show symptoms in adulthood, was excluded from the primary analyses because the *Z*-statistic for the single nucleotide polymorphism (SNP)–based heritability was below the recommended cutoff for producing interpretable genetic correlation (r_g) estimates (6). Information on the genotyping, quality control, and GWAS procedures can be found in the original article by Rajagopal *et al.* (5). The $ADHD_{child}$ and $ADHD_{adult}$ GWASs were used for all analyses, including genome-wide and gene expression analyses.

External Traits. We selected 98 phenotypes from 6 broad domains (encompassing psychiatric, cognitive, health, risk-taking, social relationship, and substance use outcomes) to examine their genetic overlap with $ADHD_{child}$ and $ADHD_{adult}$. For each phenotype, we selected the most well-powered, publicly available GWAS of unrelated individuals of European ancestry (Table S1). Details about dataset quality control can be found in the Supplement.

Genomic Structural Equation Modeling

We used genomic structural equation modeling (Genomic SEM) to estimate the r_g between each of the 98 external traits and the 2 ADHD subgroups to identify significant differences between childhood and adulthood ADHD. This was achieved by first estimating the r_g between traits using a multivariable version of linkage disequilibrium score regression (6) that estimates r_g based on GWAS summary statistics. Then we estimated models in which the r_g across the ADHD subgroups was freely estimated, while the r_g with the external trait was fixed to equality across the subgroups (Figure S1). This produced a model with 1 *df*, such that the χ^2 statistic for this model specification reflects the level of misfit resulting from the equality constraint. Thus, significant model χ^2 estimates represent external traits with significantly different levels of genetic overlap across the ADHD subgroups. A Bonferroni correction was used to correct for multiple testing by dividing the standard .05 significance threshold by the 98 traits ($p < 5.10 \times 10^{-4}$). The primary analyses presented herein reflect the model χ^2 estimates when using the genetic correlation and sampling correlation matrix (i.e., the standardized matrix of sampling dependencies) as input. Results using unstandardized estimates with the genetic and sampling covariance matrices as input can be found in Table S3. Results for stratified Genomic SEM, seeking to identify specific biological categories (i.e., functional annotations) associated with shared or unique risk pathways across the ADHD subgroups, are presented in the Supplement (Figure S2; Tables S2–S4).

Internalizing Factor Model

Many external traits that exhibited significantly stronger r_g with $ADHD_{adult}$ reflect traits in the internalizing domain. Given this trend, we conducted a set of follow-up analyses, including 2 sets of replications (detailed in the Supplement), for an internalizing factor ($F_{internalizing}$). The internalizing domain describes disorders characterized by symptoms of sadness, worry, and fear (7). Consistent with the prior literature, we defined $F_{internalizing}$ using major depressive disorder (MDD) (8), anxiety (ANX) (9), and posttraumatic stress disorder (10). This is in contrast with externalizing disorders, which include ADHD, conduct disorder, and substance use disorder among others (11). We used $F_{internalizing}$ to first confirm that the larger genetic overlap with $ADHD_{adult}$ that we observed for individual internalizing traits also holds for this latent internalizing factor (Figure S3). To further clarify this set of results, we ran 2 follow-up models testing whether the r_g between $ADHD_{child}$ or $ADHD_{adult}$ and internalizing disorders was equal to the r_g observed between persistent ADHD and the internalizing factor.

We went on to examine whether the significant differences between $ADHD_{child}$ and $ADHD_{adult}$ on other external traits were accounted for by the genetic overlap between $ADHD_{adult}$ and the internalizing space. To this end, we specified a model in which $F_{internalizing}$ predicted both childhood- and adulthood-diagnosed ADHD and the external traits to estimate differences in genetic overlap (applying a Bonferroni correction) when removing shared variance with $F_{internalizing}$ (Figure S4).

Transcriptome-Wide SEM

Transcriptome-wide SEM (T-SEM) (12) was used to identify genes whose expression was shared or unique across ADHD

subgroups. We first applied FUSION (13) to perform a univariate transcriptome-wide association study (TWAS) for each subgroup. FUSION imputes the relationship between gene expression and a trait of interest using TWAS weights that reflect the associations between genotypes and gene expression levels from an external sample, accounting for age, sex, and ancestry. TWAS weights are estimated in FUSION by selecting the model that yields the largest variance explained between the predicted and observed expression models using 5-fold cross-validation. Evaluated models reflect best linear unbiased predictor, Bayesian sparse linear model, elastic-net regression, lasso regression, and single best expression quantitative trait loci. We included 16 sets of separately analyzed weights reflecting 1) 13 brain tissue weights from the Genotype-Tissue Expression Project (GTEx version 8) (14), 2) two dorsolateral prefrontal cortex weights from the CMC (Common Mind Consortium) (15), and 3) one set of prefrontal cortex weights from PsychEncode (16). This resulted in 73,839 expression-imputed genes across the different tissues.

Gene expression estimates from the TWAS output were then combined with the linkage disequilibrium score regression covariance matrix to estimate the effect of gene expression on a general ADHD factor. Additionally, we estimated the Q_{Gene} heterogeneity statistic, which pulls out genes that do not conform to the factor model (Figure S5). In the current analyses, Q_{Gene} identifies genes whose expression is likely unique to either childhood- or adult-diagnosed ADHD. Hits for Q_{Gene} were defined using the Bonferroni-corrected threshold of $p < 6.77 \times 10^{-7}$. Hits on the ADHD factor were defined using the same significance threshold and additionally excluded any Q_{Gene} hits to control for false positives. We consider these false positives because the Q_{Gene} statistic is specifically designed to identify genes whose expression does not operate via the general ADHD factor.

Power analyses for Q_{Gene} and the analysis of the combined factor of $ADHD_{child}$ and $ADHD_{adult}$ are described in the Supplement. We also conducted follow-up analyses for gene sets significantly associated with the ADHD factor using an overrepresentation analysis performed with the *WebGestalt* R package. The significance threshold of .05 was Bonferroni corrected for 211 external gene sets that were tested in association with our gene set ($p < 2.37 \times 10^{-4}$).

RESULTS

Genomic SEM Reveals Divergent Genetic Correlations

The r_g between $ADHD_{child}$ and $ADHD_{adult}$ was 0.76 (SE = 0.06), which was significantly different from 0 and 1, thereby indicating both shared and unique genetic architecture across these subgroups. Consistent with this shared genetic architecture, we observed several external traits that were sizably and significantly associated with both subgroups, including migraines, aggression, and smoking outcomes (Figures S6–S8). In addition, we did not observe significant differences for medical, substance use traits, or circadian rhythms (Figure S9).

Consistent with genetic divergence across these subgroups, we identified 8 external traits with significantly different r_g for $ADHD_{child}$ and $ADHD_{adult}$ (Figure 1; standardized results in Table S5 and unstandardized results in Table S6). These 8 traits included the most recent aggregate ADHD GWAS (17), which uses both $ADHD_{child}$ and $ADHD_{adult}$ subgroups. We found that the genetic signal for this combined ADHD GWAS overlapped most strongly with $ADHD_{child}$ (r_{g_Child} = 0.95 [SE = 0.05]) compared with $ADHD_{adult}$ (r_{g_Adult} = 0.87 [SE = 0.06]; $p_{difference} = 4.22 \times 10^{-4}$).

Within the cognitive domain, we observed larger negative correlations with educational attainment (EA) (18) for $ADHD_{adult}$ ($r_{g\_Adult} = -0.63$ [0.04]) than for $ADHD_{child}$ ($r_{g\_Child} = -0.48$ [0.03]; $p_{difference} = 7.12 \times 10^{-9}$). Noncognitive skills of EA, which reflect the genetic component of EA that does not overlap with cognitive performance (19), showed a significantly stronger negative genetic association with $ADHD_{adult}$ ($r_{g\_Adult} = -0.49$ [0.04]) than $ADHD_{child}$ ($r_{g\_Child} = -0.31$ [0.03]; $p_{difference} = 2.21 \times 10^{-7}$). A childhood diagnosis was also more strongly associated with reaction time (20) ($r_{g\_Adult} = -0.06$ [0.04] and r_{g_Child} = 0.12 [0.04]; $p_{difference} = 5.72 \times 10^{-6}$). However, we did not observe significant differences for an overall cognitive ability factor (general factor of intelligence, i.e., *g*-factor) (20) defined by 7 cognitive outcomes from the UK Biobank.

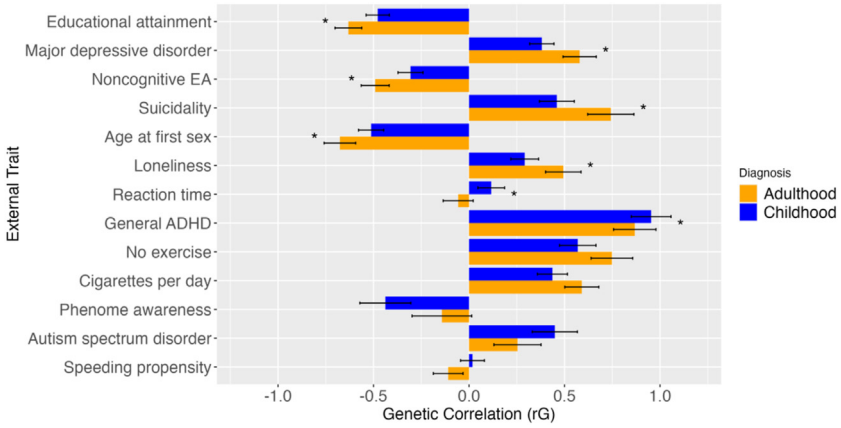

Figure 1. Genetic correlations of adulthood- and childhood-diagnosed ADHD with external traits. Bonferroni-corrected significant differences between adulthood- and childhood-diagnosed ADHD with the respective external traits are denoted with a *, and error bars display 1.96×standard error. ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment.

Within the risk-taking domain, age at first sexual intercourse (21) showed a stronger negative relationship with $ADHD_{adult}$ ($r_{g\_Adult} = -0.68$ [0.04] and $r_{g\_Child} = -0.51$ [0.03]; $p_{difference} = 1.04 \times 10^{-6}$). The psychiatric traits and correlates revealed that MDD (8) had a stronger positive r_g with $ADHD_{adult}$ ($r_{g\_Adult} = 0.58$ [0.04]) than with $ADHD_{child}$ ($r_{g\_Child} = 0.38$ [0.03]; $p_{difference} = 6.08 \times 10^{-8}$). Similarly, the genetic signal for suicide attempts (22) overlapped more strongly with $ADHD_{adult}$ ($r_{g\_Adult} = 0.74$ [0.06] and $r_{g\_Child} = 0.46$ [0.05]; $p_{difference} = 2.88 \times 10^{-7}$). Finally, we highlight the fact that in the interpersonal domain, $ADHD_{adult}$ ($r_{g\_Adult} = 0.49$ [0.05]) was more strongly associated with loneliness (23) than $ADHD_{child}$ ($r_{g\_Child} = 0.29$ [0.04]; $p_{difference} = 2.55 \times 10^{-6}$). Sensitivity analyses were conducted by estimating the r_g with the 8 significantly divergent external traits in odd and even chromosomes. These results revealed that MDD and suicide attempts showed significant divergences at the same Bonferroni significance threshold in both sets of chromosomes, while 5 traits were significant in either the odd or even chromosomes, and loneliness was not significant for either set of chromosomes (Table S7).

Adulthood-Diagnosed ADHD Is More Strongly Associated With Internalizing

Results for loneliness, suicide attempts, and MDD can collectively be conceptualized as indexing higher levels of genetic overlap for $ADHD_{adult}$ with the internalizing space. Moreover, the genetic signals for MDD, ANX, and posttraumatic stress disorder are all strongly overlapping. Therefore, we leveraged the ability of Genomic SEM to model latent genomic risk factors to examine genetic overlap with $F_{internalizing}$ defined by these 3 disorders. The χ^2 difference test revealed that the significantly larger genetic overlap with $ADHD_{adult}$ that we observed for individual internalizing traits also held for this latent internalizing factor ($r_{g\_Adult} = 0.64$ [0.05] and $r_{g\_Child} = 0.44$ [0.04], $p_{difference} = 5.67 \times 10^{-7}$; Figure 2). This finding replicated across two, semi-independent samples for the internalizing disorders (see the Supplement). Although the χ^2 difference test was not significant for the comparisons that included the persistent ADHD phenotype with the child ($p_{difference} = 9.64 \times 10^{-1}$) or adult ($p_{difference} = 2.41 \times 10^{-3}$) subgroup, the point estimate was more similar to that of the adult subgroup ($r_{g\_Persistent} = 0.65$ [0.05]) (Figure S10).

Across a set of 3 analyses, a main analysis and 2 replications as detailed in the Supplement, we examined whether the significant differences between $ADHD_{child}$ and $ADHD_{adult}$ on other external traits are accounted for by the genetic overlap between $ADHD_{adult}$ and $F_{internalizing}$. When controlling for shared genetic variance with internalizing, 4 traits were found to have significantly different levels of genetic overlap across $ADHD_{child}$ and $ADHD_{adult}$ in the main analysis and both replications (Table S8). This included 3 of the traits—noncognitive skills of EA, a general ADHD diagnosis, and reaction time—that were identified in the model without internalizing, including an even larger difference between child and adult ADHD with general ADHD. Additionally, autism spectrum disorder (ASD) (24) emerged, evidencing a stronger association with $ADHD_{child}$. Notably, the r_g with ASD and $ADHD_{adult}$ when controlling for internalizing was near 0 ($r_{g\_Adult} = < 0.01$ [0.07]) (Figure 3). Conversely, the significant differences

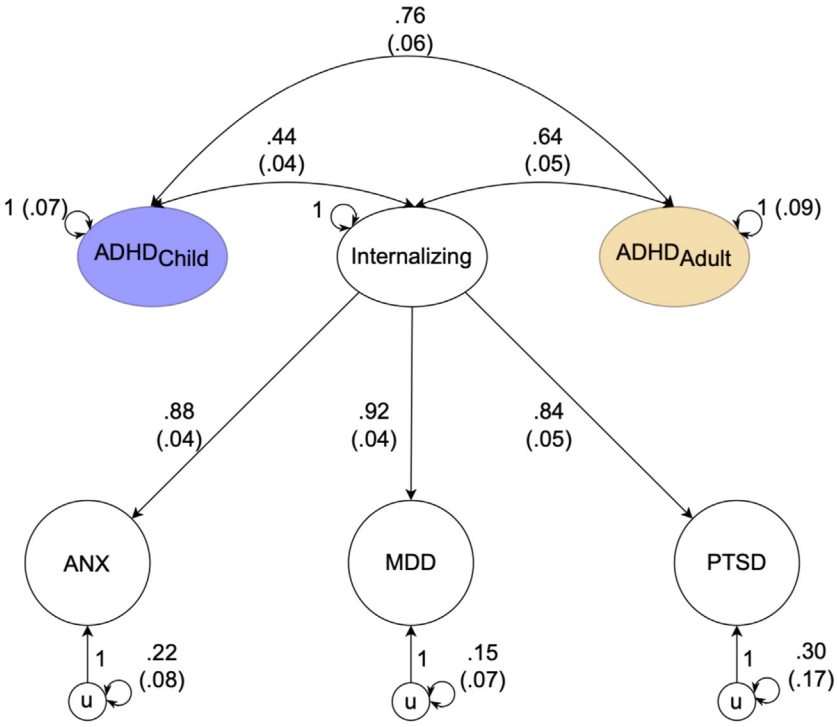

Figure 2. Path diagram of genetic correlations of adulthood- and childhood-diagnosed ADHD with the internalizing factor. Path diagram of the model used in genomic structural equation modeling to confirm that the pattern of larger genetic overlap with adulthood-diagnosed ADHD that we observe for individual internalizing traits also holds for this latent internalizing factor. In this model, internalizing is a common genetic factor of the genetic components of ANX, MDD, and PTSD and u is the residual genetic variance in these phenotypes that is not explained by the internalizing factor. Observed variables are represented as squares, and latent variables are represented as circles. The genetic component of each phenotype is represented with a circle because the genetic component is a latent variable that is not directly measured but is inferred using linkage disequilibrium score regression. Single-headed arrows are regression relations; double-headed arrows connecting back to the same origin are variances; and double-headed arrows connecting 2 variables are correlations. Paths labeled 1 are fixed to 1. ADHD, attention-deficit/hyperactivity disorder; ANX, anxiety; MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

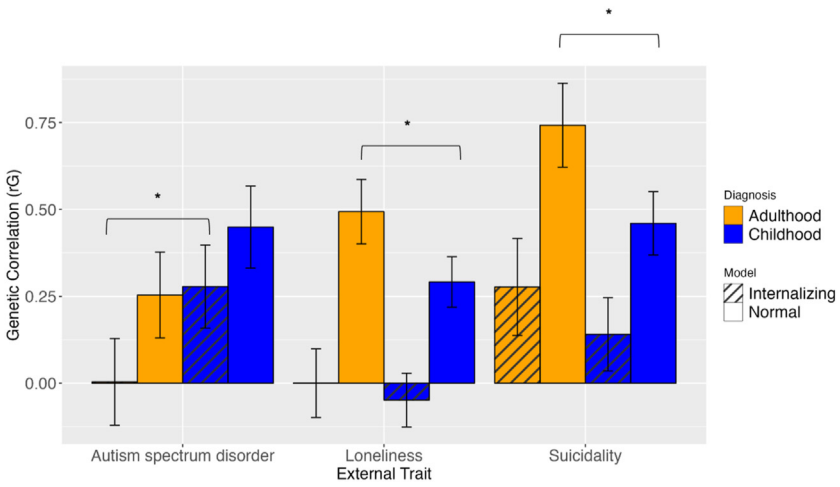

Figure 3. Genetic correlations of adulthood- and childhood-diagnosed ADHD with externalizing traits. Results without accounting for the overlap of the internalizing factor with ADHD are displayed in the solid bars, and results accounting for the overlap of the internalizing factor with ADHD are displayed in the striped bars. Error bars display 1.96×standard error. ADHD, attention-deficit/hyperactivity disorder.

in r_g with $ADHD_{adult}$ and $ADHD_{child}$ in suicidal behavior (r_{g_Adult} = 0.28 [0.07] and r_{g_Child} = 0.14 [0.05]; $p_{difference} = 3.08 \times 10^{-3}$) and loneliness ($r_{g\_Adult}$ = 0.00 [0.05] and r_{g_Child} = −0.05 [0.04]; $p_{difference} = 9.74 \times 10^{-2}$) became nonsignificant after accounting for the overlap with $F_{internalizing}$ (Figure 3).

T-SEM Pinpoints Genes Associated With General ADHD

Univariate TWAS results revealed 2 genes whose expression was significantly associated with ADHD diagnosed in adulthood and 19 genes for ADHD diagnosed in childhood (Table 1). Power simulations for T-SEM are described in the Supplement. These simulations indicated approximately 93% power at a Bonferroni-corrected significance threshold to detect large gene expression effects on the ADHD factor and 100% power for Q_{Gene} to detect genes with strong opposite direction effects on the ADHD indicators, but limited power for Q_{Gene} to detect genes with larger, but directionally concordant, effects (Tables S9 and S10).

T-SEM identified 22 unique genes whose expression was associated with a general ADHD factor (Figure 4; Table S11). Highlighting that T-SEM of the ADHD factor was working as expected to capture genes whose expression is shared across the ADHD subgroups, these genes were all either significant or nearly significant for the univariate TWAS of each ADHD trait (Figure S11). T-SEM also allowed for making novel discoveries by leveraging the shared power across the ADHD subgroups: the factor results included 15 genes that were novel relative to the univariate TWAS of the subgroups and 11 genes that were novel relative to a TWAS of general ADHD (Table S12) disregarding age at diagnosis. No significant Q_{Gene} hits (Table S13 for top Q_{Gene} results) or *WebGestalt* gene sets were identified.

Table 1. Significant Univariate TWAS Hits

Gene	Tissue	CHR	h^2	TWAS *Z*	TWAS *p* Value
Adulthood					
MST1R	Cortex	3	0.13	5.10	3.42×10^{-7}
C1QTNF7	Putamen	4	0.22	−5.01	5.56×10^{-7}
Childhood					
LINC02060	Cerebellum	5	0.15	−6.26	3.94×10^{-10}
KDM4A	Prefrontal cortex	1	0.03	−5.69	1.26×10^{-8}
CTC-498M16.4	Cerebellum	5	0.16	−5.65	1.62×10^{-8}
MED8	Hippocampus	1	0.24	−5.50	3.72×10^{-8}
RP5-984P4.6	Nucleus accumbens	20	0.12	−5.37	7.96×10^{-8}
TMEM125	Putamen	1	0.18	5.14	2.74×10^{-7}
CDC20	Prefrontal cortex	1	0.14	5.13	2.89×10^{-7}
RP11-7O11.3	Caudate	1	0.22	−5.08	3.71×10^{-7}
ST3GAL3	Prefrontal cortex	1	0.11	5.02	5.05×10^{-7}
FEZ2	Cerebellar hemisphere	2	0.55	5.00	5.61×10^{-7}

Significant TWAS hits for adulthood- and childhood-diagnosed ADHD ordered by their *p* value. Each row reports the tissue they are expressed in, the CHR, estimated *cis*-heritability of gene expression provided by the FUSION output (h^2), and the univariate TWAS *Z*-statistics and *p* values.

ADHD, attention-deficit/hyperactivity disorder; CHR, chromosome; TWAS, transcriptome-wide association study.

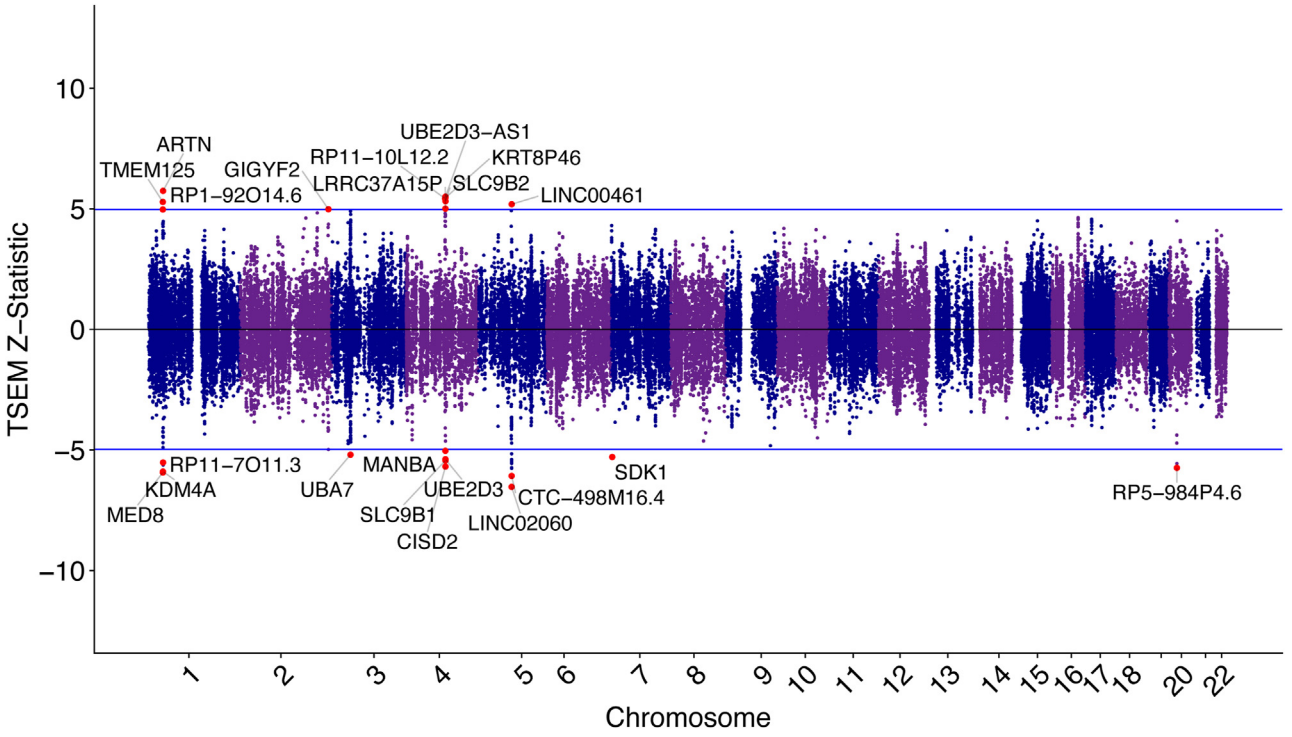

Figure 4. Miami plot for gene expression hits for the combined factor of childhood- and adulthood-diagnosed ADHD. The upper and lower blue lines represent the Bonferroni-corrected significance threshold. Genes surpassing the upper and lower cutoff are upwardly and downwardly regulated, respectively, in the ADHD factor. The most significant genes across tissue types are labeled and colored as red dots. ADHD, attention-deficit/hyperactivity disorder; TSEM, transcriptome-wide structural equation modeling.

DISCUSSION

The current study used Genomic SEM and its extensions to investigate the degree to which the genetic signal for childhood- and adulthood-diagnosed ADHD are shared and unique at multiple levels of biological analysis. To the best of our knowledge, this is only the second genomic examination of childhood- and adulthood-diagnosed ADHD and the first multivariate examination expanding upon the original study from Rajagopal *et al.* (5) in several important ways. At the genome-wide level, we estimated r_g between each subgroup and 98 external traits spanning psychiatric, cognitive, health, risk-taking, social relationship, and substance use outcomes, whereas the original study examined relationships with 13 traits. Using a model χ^2 difference test, we identified 8 traits with significantly divergent genetic overlap with the 2 ADHD phenotypes. Because many of these traits can be described as correlates or indicators of the internalizing dimension, we then used the unique multivariate modeling capabilities of Genomic SEM to examine genetic overlap with a latent internalizing factor. Primary and replication analyses for $ADHD_{adult}$ revealed a much larger, positive r_g with $F_{internalizing}$ and that removing genetic overlap with $F_{internalizing}$ reduced the r_g with ASD to near 0. Interpretations of these findings are discussed below. Finally, we applied T-SEM and stratified genomic SEM, 2 recently introduced multivariate genomic methods, to identify 22 unique genes and 3 functional annotations (see the Supplement), respectively, that are associated with shared genetic pathways across both childhood- and adulthood-diagnosed ADHD. These findings are considered in greater detail below.

Genetic Correlations With External Traits

At the level of genetic overlap with external correlates, the primary differences were identified for cognitive and internalizing outcomes. Within the cognitive domain, $ADHD_{adult}$ showed a stronger negative association with EA and noncognitive skills of EA. This divergent relationship did not hold for a range of cognitive traits, including a *g*-factor of general intelligence. The difference in findings between the cognitive traits and the noncognitive skills that play a role in EA then indicates that adult-diagnosed ADHD genetically overlaps specifically with the noncognitive rather than the cognitive aspects that lead to success in school settings.

Within the internalizing space, we found that $ADHD_{adult}$ has a sizable and more positive association with MDD, suicidal behavior, loneliness, and $F_{internalizing}$ defined by MDD, posttraumatic stress disorder, and ANX.

Internalizing Follow-Up Models Reveal Possible Mechanisms for Divergence

One possible interpretation of the findings for the internalizing traits is that adult-diagnosed ADHD can, in some instances, reflect a misdiagnosis that occurs at higher rates than in children. This is supported by the fact that the internalizing space shares overlapping symptoms with externalizing disorders, such as ADHD, including difficulty concentrating and

restlessness. Moreover, longitudinal studies indicate that retrospective recall of ADHD symptoms is at best only modestly correlated with childhood ratings (25,26). An alternative interpretation is that ADHD diagnosed in adulthood is not a misdiagnosis, but rather more comorbid with internalizing disorders. For example, it could be that ADHD diagnosed in adulthood is more disruptive to daily living or that the absence of a diagnosis until a later life stage increases risk for other disorders. In support of this, adults with ADHD often display high rates of general mental health symptoms, such as anxiety and depression (27). However, we observed high levels of genetic overlap with a latent factor of internalizing (r_{g_Adult} = 0.64 [0.05]) even when using separate participant samples. Thus, some causal link between ADHD and internalizing traits is unlikely to explain the entirety of this strong genetic correlation because this would require ADHD to be one of the primary risk factors for internalizing traits in the population (or vice versa).

Follow-up models accounting for the shared variance with $F_{internalizing}$ provided 2 additional sets of findings for interpreting the emergent etiological picture. First, we found that the $F_{internalizing}$ explains the larger genetic overlap between adult-diagnosed ADHD and 2 clinical correlates of internalizing: loneliness and suicidal behavior. Second, childhood-diagnosed ADHD showed a much stronger association with both general ADHD and ASD than adult-diagnosed ADHD when controlling for shared variance with internalizing. Moreover, the r_g with adult-diagnosed ADHD and ASD was estimated to be near 0 when controlling for shared genetic variance with $F_{internalizing}$. This indicates that the neurodevelopmental signal captured in the adult-diagnosed ADHD GWAS is greatly diminished, or entirely absent when removing shared genetic variance with internalizing, which further supports a hypothesis of increased levels of misdiagnosis during adulthood.

Evidence against the misdiagnosis interpretation came from follow-up models examining the correlation with persistent ADHD and internalizing. We observed that the point estimate for the r_g with internalizing was more similar for adulthood and persistent ADHD than for $ADHD_{child}$. Although the difference between persistent ADHD and $ADHD_{child}$ was not significant, we were generally underpowered for analyses using the persistent phenotype. Because persistent ADHD is arguably less likely to reflect misdiagnosis given its original diagnosis in childhood, these tentative results indicate that internalizing disorders may play a significant role in fostering the persistence of ADHD into adulthood. However, it is important to note that these findings present an alternative perspective rather than definitively pointing to one mechanism over the other and should be reevaluated once power is sufficient. Another possible mechanism for this overlap between internalizing and adulthood-diagnosed ADHD is sex differences in symptom patterns as well as age at diagnosis. Notably, 41% of the adulthood-diagnosed cases were female, in contrast to 23% of the childhood-diagnosed cases (5). Irrespective of whether a misdiagnosis or a clinically relevant distinction between ADHD diagnosed in childhood and ADHD diagnosed in adulthood is the cause for their divergence, etiological differences between the two ages at diagnosis may inform the way that clinical care is provided based on age at diagnosis.

T-SEM Analyses Identify Genes Associated With Shared ADHD Risk

Highlighting the ability of multivariate approaches to yield novel discoveries, T-SEM identified 15 novel genes relative to univariate TWAS of childhood- or adult-diagnosed ADHD and 11 novel genes relative to a TWAS of general ADHD. The 5 most significant genes have previously been linked to ADHD and related phenotypes. *LINC02060* and *CTC-498M16.4* have been linked to ADHD, and *CTC-498M16.4* has been linked to additional phenotypes, including depression and sleep characteristics (28,29). The *MED8* gene has been found to bind to regulatory elements and is a gene of interest for both ADHD and schizophrenia susceptibility (30,31). The *KDM4A* gene is related to disruptive behavior disorders in the context of ADHD (32). Finally, the *ARTN* gene supports the survival, development, methylation, and differentiation of neurons and has been linked to ADHD and schizophrenia (28,31,33). Identifying genes in the contexts of these analyses clarifies their role in influencing shared pathways across the 2 ADHD subgroups.

Among the TWAS hits and T-SEM hits of the factor, we found multiple noncoding RNA genes (e.g., *LINC00461* and *LINC02060*). Noncoding RNA genes are of interest in brain evolution (34) as well as normal human brain development (35) due to their high expression rate in the brain and their role in regulating gene expression and modulation. Given their relevance to brain development and function, they become particularly intriguing in the context of ADHD, a neurodevelopmental disorder that emerges during early life, making them compelling candidates for further investigation in the context of ADHD.

Likely due to limited power, no genes were significant for the Q_{Gene} heterogeneity statistic applied to identify genes with divergent association with childhood- and adulthood-diagnosed ADHD. The *DNM1* and *CRIM1* genes showed some of the strongest divergence, with stronger associations with adulthood- and childhood-diagnosed ADHD, respectively. *DNM1* has been associated with developmental delay and epilepsy (36), and *CRIM1* has been identified as playing a role in the development, differentiation, and survival of motor neurons (37).

Limitations

All summary statistics in this study are limited to European ancestry because sample sizes are lacking for other ancestries. However, ADHD is a global problem (38), and to understand this disorder and its relationship with other disorders, traits, and behaviors, we need to expand our research in underrepresented populations. The childhood- and adulthood-diagnosed ADHD summary statistics used in this study largely overlap with the general ADHD summary statistics used by Demontis *et al.* (17). The current study used the same set of controls and has a case overlap of 38.5% of the childhood-diagnosed and 18% of the adulthood-diagnosed cases. The absence of Q_{Gene} hits in T-SEM analyses likely reflects limited power. Our power analysis demonstrated that power to detect

Q_{Gene} hits was low, apart from the most extreme circumstance when gene expression effects on childhood- and adulthood-diagnosed ADHD were strong and in opposing directions. Although univariate TWAS revealed more significant hits for childhood- than for adulthood-diagnosed ADHD, this is likely an artifact of the difference in power in the 2 subgroups, where childhood ADHD had approximately twice as many cases in the contributing GWAS. Therefore, the T-SEM and TWAS results should be reevaluated as the ADHD GWAS sample sizes increase. Finally, our analyses, which were reliant on genetic correlations, share limitations inherent to such genetic correlations. For example, genetic correlations can be upwardly biased by cross-trait assortative mating (39). Cross-trait assortative mating is the mechanism in which individuals who score higher than average on one trait mate with others who score higher (or lower) than average on a different trait. This limitation requires special attention because these biases are of different magnitudes between any pair of included traits. However, because the genetic correlations of many traits included, especially psychiatric traits, are substantial, it is highly unlikely that they are entirely explained by cross-trait assortative mating (40).

Conclusions

Although effective treatment approaches to ADHD are available, strategies for finding the right treatment are often based on a trial-and-error approach. This can lead patients to give up before finding the appropriate intervention (41). Disentangling pathways, symptoms, and comorbidities specific to different subtypes and clinical presentations of ADHD, such as childhood- and adulthood-diagnosed subtypes, may help improve treatment outcomes by more quickly identifying medications and therapies that are likely to be effective for specific groups of individuals. The multivariate framework used here, which examines genetic convergence and divergence across varying levels of biological granularity (genome-wide, functional, and gene expression), may also serve as a template for future work investigating the etiological utility of distinguishing between subgroups within disorders. The current findings indicate that ADHD diagnosed in adulthood is far more genetically similar to internalizing disorders and clinical correlates than childhood-diagnosed ADHD. Whether this reflects pervasive misdiagnosis or distinct patterns of genetic risk across these 2 groups, identifying these differences highlights the clinical and etiological importance of distinguishing these subgroups within this overarching disorder class.

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ARTICLE INFORMATION

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REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007): The worldwide prevalence of ADHD: A systematic review and meta-regression analysis. Am J Psychiatry 164:942–948.
2. Baselmans BML, Yengo L, Van Rheenen W, Wray NR (2021): Risk in relatives, heritability, SNP-based heritability, and genetic correlations in psychiatric disorders: A review. Biol Psychiatry 89:11–19.
3. Miller CJ, Newcorn JH, Halperin JM (2010): Fading memories: Retrospective recall inaccuracies in ADHD. J Atten Disord 14:7–14.
4. Agnew-Blais JC, Belsky DW, Caspi A, Danese A, Moffitt TE, Polanczyk GV, *et al.* (2021): Polygenic risk and the course of attention-deficit/hyperactivity disorder from childhood to Young adulthood: Findings from a nationally representative cohort. J Am Acad Child Adolesc Psychiatry 60:1147–1156.
5. Rajagopal VM, Duan J, Vilar-Ribó L, Grove J, Zayats T, Ramos-Quiroga JA, *et al.* (2022): Differences in the genetic architecture of common and rare variants in childhood, persistent and late-diagnosed attention-deficit hyperactivity disorder. Nat Genet 54:1117–1124.
6. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, *et al.* (2015): An atlas of genetic correlations across human diseases and traits. Nat Genet 47:1236–1241.
7. Lahey BB, Rathouz PJ, Van Hulle C, Urbano RC, Krueger RF, Applegate B, *et al.* (2008): Testing structural models of DSM-IV symptoms of common forms of child and adolescent psychopathology. J Abnorm Child Psychol 36:187–206.
8. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, *et al.* (2019): Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 22:343–352.
9. Purves KL, Coleman JRI, Meier SM, Rayner C, Davis KAS, Cheesman R, *et al.* (2020): A major role for common genetic variation in anxiety disorders. Mol Psychiatry 25:3292–3303.
10. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen CY, Choi KW, *et al.* (2019): International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nat Commun 10:4558.
11. Waldman ID, Poore HE, Van Hulle C, Rathouz PJ, Lahey BB (2016): External validity of a hierarchical dimensional model of child and adolescent psychopathology: Tests using confirmatory factor analyses and multivariate behavior genetic analyses. J Abnorm Psychol 125:1053–1066.
12. Grotzinger AD, de la Fuente J, Davies G, Nivard MG, Tucker-Drob EM (2022): Transcriptome-wide and stratified genomic structural equation modeling identify neurobiological pathways shared across diverse cognitive traits. Nat Commun 13:6280.
13. Gusev A, Ko A, Shi H, Bhatia G, Chung W, Penninx BWJH, *et al.* (2016): Integrative approaches for large-scale transcriptome-wide association studies. Nat Genet 48:245–252.
14. GTEx Consortium (2013): The Genotype-Tissue Expression (GTEx) project. Nat Genet 45:580–585.
15. Hoffman GE, Bendl J, Voloudakis G, Montgomery KS, Sloofman L, Wang YC, *et al.* (2019): CommonMind Consortium provides transcriptomic and epigenomic data for Schizophrenia and bipolar disorder. Sci Data 6:180.
16. Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, *et al.* (2018): Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science 362:eaat8127.
17. Demontis D, Walters GB, Athanasiadis G, Walters R, Therrien K, Nielsen TT, *et al.* (2023): Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. Nat Genet 55:198–208.

18. Okbay A, Wu Y, Wang N, Jayashankar H, Bennett M, Nehzati SM, *et al.* (2022): Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. Nat Genet 54:437–449.
19. Demange PA, Malanchini M, Mallard TT, Biroli P, Cox SR, Grotzinger AD, *et al.* (2021): Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction. Nat Genet 53:35–44.
20. de la Fuente J, Davies G, Grotzinger AD, Tucker-Drob EM, Deary IJ (2021): A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data. Nat Hum Behav 5:49–58.
21. Watanabe K, Stringer S, Frei O, Umićević Mirkov M, de Leeuw C, Polderman TJC, *et al.* (2019): A global overview of pleiotropy and genetic architecture in complex traits. Nat Genet 51:1339–1348.
22. Mullins N, Kang J, Campos AI, Coleman JRI, Edwards AC, Galfalvy H, *et al.* (2022): Dissecting the shared genetic architecture of suicide attempt, psychiatric disorders, and known risk factors. Biol Psychiatry 91:313–327.
23. Day FR, Ong KK, Perry JRB (2018): Elucidating the genetic basis of social interaction and isolation. Nat Commun 9:2457.
24. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al.* (2019): Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51:431–444.
25. Breda V, Rohde LA, Menezes AMB, Anselmi L, Caye A, Rovaris DL, *et al.* (2020): Revisiting ADHD age-of-onset in adults: To what extent should we rely on the recall of childhood symptoms? Psychol Med 50:857–866.
26. Von Wirth E, Mandler J, Breuer D, Döpfner M (2021): The accuracy of retrospective recall of childhood ADHD: Results from a longitudinal study. J Psychopathol Behav Assess 43:413–426.
27. Skirrow C, Asherson P (2013): Emotional lability, comorbidity and impairment in adults with attention-deficit hyperactivity disorder. J Affect Disord 147:80–86.
28. Liao C, Laporte AD, Spiegelman D, Akçimen F, Joober R, Dion PA, Rouleau GA (2019): Transcriptome-wide association study of attention deficit hyperactivity disorder identifies associated genes and phenotypes. Nat Commun 10:4450.
29. O'Connell KS, Frei O, Bahrami S, Smeland OB, Bettella F, Cheng W, *et al.* (2021): Characterizing the genetic overlap between psychiatric disorders and sleep-related phenotypes. Biol Psychiatry 90:621–631.
30. Alonso-Gonzalez A, Calaza M, Rodriguez-Fontenla C, Carracedo A (2019): Gene-based analysis of ADHD using Pascal: A biological insight into the novel associated genes. BMC Med Genomics 12:143.
31. Reay WR, Cairns MJ (2020): Pairwise common variant meta-analyses of schizophrenia with other psychiatric disorders reveals shared and distinct gene and gene-set associations. Transl Psychiatry 10:134.
32. Demontis D, Walters RK, Rajagopal VM, Waldman ID, Grove J, Als TD, *et al.* (2021): Risk variants and polygenic architecture of disruptive behavior disorders in the context of attention-deficit/hyperactivity disorder. Nat Commun 12:576.
33. Ilieva M, Nielsen J, Korshunova I, Gotfryd K, Bock E, Pankratova S, Michel TM (2019): Artemin and an artemin-derived peptide, Artefin, induce neuronal survival, and differentiation through ret and NCAM. Front Mol Neurosci 12:47.
34. Zimmer-Bensch G (2019): Emerging roles of Long non-coding RNAs as drivers of brain evolution. Cells 8:1399.
35. Nie JH, Li TX, Zhang XQ, Liu J (2019): Roles of non-coding RNAs in normal human brain development, brain tumor, and neuropsychiatric disorders. Noncoding RNA 5:36.
36. Michetti C, Falace A, Benfenati F, Fassio A (2022): Synaptic genes and neurodevelopmental disorders: From molecular mechanisms to developmental strategies of behavioral testing. Neurobiol Dis 173: 105856.
37. Kolle G, Georgas K, Holmes GP, Little MH, Yamada T (2000): CRIM1, a novel gene encoding a cysteine-rich repeat protein, is developmentally regulated and implicated in vertebrate CNS development and organogenesis. Mech Dev 90:181–193.
38. GBD (2019): Mental Disorders Collaborators (2022): Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 9:137–150.
39. Border R, Athanasiadis G, Buil A, Schork AJ, Cai N, Young AI, *et al.* (2022): Cross-trait assortative mating is widespread and inflates genetic correlation estimates. Science 378:754–761.
40. Grotzinger AD, Keller MC (2022): Potential bias in genetic correlations. Science 378:709–710.
41. Mamiya PC, Arnett AB, Stein MA (2021): Precision medicine care in ADHD: The case for neural excitation and inhibition. Brain Sci 11:91.