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Genome-wide analyses of attention deficit hyperactivity disorder identify 27 risk loci, refine the genetic architecture, and implicate several cognitive domains

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Analysis: D.D., G.B.W., G.A., R.W., K.T., L.F., G.V., J.B., B.Z., W.Z., J.D., S.H.M. and T.T.N. **Sample and/or data provider and processing:** D.D., G.B.W., J.G., T.D.A., J.D., F.K.S., J.B.-G., M.B.-H., O.O.G., G.B., K.D., G.S.H., ADHD Working Group of the Psychiatric Genomics Consortium (PGC), iPSYCH-Broad Consortium, E.A., G.E.H., M.N., O.M., D.M.H., P.B.M., M.J.D., H.S., T.W., B.M.N., K.S. and A.D.B. **Writing:** D.D., G.B.W., K.T., G.A., G.V., J.B., H.S. and A.D.B. **Core revision:** D.D., G.B.W., G.A., R.W., K.T., G.V., J.B., S.D., J.M., M.R., F.K.S., D.I.B., M.S.A., N.R.M., D.H., S.E.M., T.Z., V.M.R., S.V.F., H.S., P.R., B.F., B.M.N., K.S. and A.D.B. **Study direction:** D.D. and A.D.B. **Study supervision:** D.D., G.B.W., H.S., P.R., B.F., T.W., B.M.N., K.S. and A.D.B. All authors contributed with critical revision of the manuscript.

COMPETING INTERESTS

B.M.N. currently serves as a member of the scientific advisory board at Deep Genomics and Neumora (previously RBNC) and consultant for Camp4 Therapeutics, Takeda Pharmaceutical, and Biogen. All deCODE affiliated authors are employees of deCODE/Amgen. The remaining authors declare no competing interests.

Code availability

No previously unreported custom computer code or algorithms were used to generate results.

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder with a major genetic component. Here we present a genome-wide association study meta-analysis of ADHD comprising 38,691 individuals with ADHD and 186,843 controls. We identified 27 genome-wide significant loci, highlighting 76 potential risk genes enriched among genes expressed particularly in early brain development. Overall, ADHD genetic risk was associated with several brain-specific neuronal sub-types and midbrain dopaminergic neurons. In exome-sequencing data from 17,896 individuals, we identified an increased load of rare protein-truncating variants in ADHD for a set of risk genes enriched with likely causal common variants, potentially implicating *SORCS3* in ADHD by both common and rare variants. Bivariate Gaussian mixture modeling estimated that 84–98% of ADHD-influencing variants are shared with other psychiatric disorders. Additionally, common variant ADHD risk was associated with impaired complex cognition such as verbal reasoning and a range of executive functions, including attention.

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder, affecting around 5% of children, and persists into adulthood in two-thirds of cases^{1,2}. It is characterized by extensive hyperactive, impulsive and/or inattentive behaviors that impair daily functioning. The disorder is associated with multiple adverse outcomes, such as injuries³, accidents⁴, depression⁵, substance use disorders⁶, aggression⁷, premature death⁸ and high rate of unemployment⁹, and has large societal costs^{10–12}.

ADHD has a major genetic component, with an estimated twin heritability of 0.74¹³. Despite this, ADHD's complex polygenic architecture makes it difficult to unravel its underlying biological causes. Previously, we discovered the first 12 genome-wide significant loci for ADHD¹⁴ in a genome-wide association study (GWAS) of 20,183 cases and 35,191 controls (here referred to as ADHD2019) that combined the first wave of data from the Danish iPSYCH¹⁵ cohort (iPSYCH1) with 11 ADHD cohorts collected by the Psychiatric Genomics Consortium (PGC). We established the role of common variants in ADHD, explaining around 22% of the variance in the phenotype. The results implicated brain-expressed genes and demonstrated considerable genetic overlap of ADHD with a range of phenotypes, e.g., within psychiatric, cognitive, and metabolic domains. Additionally, a recent cross-disorder GWAS of ADHD and autism¹⁶ has identified shared and differentiating loci and showed that individuals with both ADHD and autism have distinctive patterns of genetic association with other traits compared to those with only a single diagnosis. This highlights that further mapping of the shared genetic risk component with other psychiatric disorders is important for understanding the complexity of the genetics underlying ADHD. Analyses of whole-exome sequencing data have shown that rare variants also contribute to the risk for ADHD¹⁷, especially in mutationally constrained genes.

To better understand the biological mechanisms underlying ADHD, it is fundamental to conduct large genetic studies, as has been demonstrated in other psychiatric disorders^{18–20}. Here we present results from an updated GWAS meta-analysis of ADHD, combining data from the newly extended Danish iPSYCH cohort, the Icelandic deCODE cohort and the PGC, almost doubling the number of cases compared with ADHD2019. We fine-map identified risk loci and integrate with functional genomics data to pinpoint potential causal genes and evaluate the burden of rare deleterious variants in top-associated genes. We characterize the polygenic architecture of ADHD and its overlap with other phenotypes by bivariate mixture modeling and perform polygenic score (PGS) analyses to test for association of ADHD-PGS with neurocognitive measures in the Philadelphia Neurodevelopmental Cohort (PNC).

RESULTS

Identification of new ADHD risk loci by GWAS meta-analysis.

We conducted a GWAS meta-analysis based on expanded data from iPSYCH (25,895 cases; 37,148 controls), deCODE genetics (8,281 cases; 137,993 controls) and published data from 10 ADHD cohorts with European ancestry collected by the PGC (4,515 cases; 11,702 controls), resulting in a total sample size of 38,691 individuals with ADHD and 186,843 controls (effective sample size ($n_{\text{eff_half}}$) = 51,568; cohorts listed in Supplementary Table 1).

The GWAS meta-analysis identified 32 independent lead variants (i.e., with a squared correlation (r^2) < 0.1 between variants) located in 27 genome-wide significant loci (Fig. 1, Table 1, locus plots in Supplementary Data 1, and forest plots in Supplementary Data 2), including 21 novel loci. No statistically significant heterogeneity was observed between cohorts (Supplementary Fig. 1). The three most strongly associated loci ($P < 5 \times 10^{-14}$) were located on chromosome 1 (in and around *PTPRF*), chromosome 5 (downstream of *MEF2C*) and chromosome 11 (downstream of *METTL15*); the latter is a novel ADHD risk locus. Four loci on chromosomes 1, 5, 11, and 20 had secondary genome-wide significant lead variants ($r^2 < 0.1$ between the index variant and the secondary lead variant within a region of 0.5 Mb), but none remained genome-wide significant in analyses conditioning on the index variant using COJO²¹ (Supplementary Table 2).

Six of the previously identified 12 loci in the ADHD2019 study¹⁴ were significant in the present study (Table 1), and the remaining six loci demonstrated P -values $< 8 \times 10^{-4}$ (Supplementary Table 3). Overall, the direction of association of the top loci (726 loci with $P < 1 \times 10^{-4}$) was consistent with the direction of association in ADHD2019 for all loci but one (Supplementary Table 4).

Genetic correlations among cohorts and SNP-heritability.

Genetic correlation analyses supported a high consistency in the phenotype across cohorts (r_g ranging from 0.82 to 0.93, Supplementary Table 5), and between iPSYCH1 and iPSYCH2 ($r_g = 0.97$; s.e. = 0.06). None of the genetic correlations were significantly different from 1. LD score regression analysis found an intercept of 1.04 (s.e. = 0.009) and ratio of 0.092 (s.e. = 0.02), the latter indicating that around 90% of the deviation from null, in the distribution of the test statistics, reflects polygenicity (QQ-plot shown in Supplementary Fig. 2). The SNP heritability (h^2_{SNP}) was estimated to 0.14 (s.e. = 0.01), which is lower than the previously reported h^2_{SNP} of 0.22¹⁴. The h^2_{SNP} for iPSYCH ($h^2_{\text{SNP}} = 0.23$; s.e. = 0.01) was in line with the previous finding, but lower h^2_{SNP} was observed for PGC ($h^2_{\text{SNP}} = 0.12$; s.e. = 0.03) and deCODE ($h^2_{\text{SNP}} = 0.08$; s.e. = 0.014). The difference in h^2_{SNP} was not caused by different sex distributions across cohorts as there were no significant differences in h^2_{SNP} between males and females in the iPSYCH and deCODE cohorts (Supplementary Table 5). Between-cohort heterogeneity in h^2_{SNP} is not unusual and has been observed in other diagnoses such as major depressive disorder²².

Mapping risk variants to genes and enrichment analyses.

To link identified risk variants to genes, we first identified sets of Bayesian credible variants for each risk locus, with each set most likely (probability > 95%) including a causal variant (Supplementary Table 6). Credible variants were subsequently linked to genes based on genomic position, information about expression quantitative trait loci (eQTLs) and chromatin interaction mapping in human brain tissue as implemented in FUMA²³ (datasets selected are listed in the Supplementary Note). We identified 76 plausible ADHD risk genes (Supplementary Table 7); four of the 76 were mapped by position alone. We found that this set of genes is significantly enriched among genes upregulated during early embryonic brain development (19th post-conceptual week; $P_{\text{one-sided}} = 0.0008$; Supplementary Fig. 3) and highly enriched for genes identified in GWASs of cognition-related phenotypes and

reproduction (Supplementary Fig. 4). The role of the genes in synapses was evaluated using SynGO data²⁴; nine genes mapped to SynGO annotations, and genes encoding integral components of the postsynaptic density membrane were borderline significantly enriched ($P = 5.43 \times 10^{-3}$; q -value 0.022; genes *PTPRF*, *SORCS3*, and *DCC*; Supplementary Fig. 5 and Supplementary Table 8). One SynGO-mapped gene was also a part of the upregulated genes during early embryonic brain development (*ARHGAP39*). Additionally, enrichment of the 76 genes in biological pathways was tested using data from 26 databases implemented in Enrichr^{25,26}. No pathways showed significant enrichment after Bonferroni correction (database significant findings can be found in Supplementary Table 9). Finally, MAGMA²⁷ gene-set analysis using gene-based P -values derived from the full GWAS summary statistics (i.e., no preselection of specific genes) did not reveal any significant findings (top gene sets can be found in Supplementary Table 10).

Transcriptome-wide association analysis.

To identify and prioritize ADHD risk genes, we also performed a transcriptome-wide association study (TWAS) of the genetically regulated gene expression using EpiXcan²⁸ and expression data from the PsychENCODE Consortium²⁹ on genes as well as isoforms detected in 924 samples from the dorsolateral prefrontal cortex (DLPFC). The TWAS identified 15 genes (Supplementary Table 11) and 18 isoforms (Supplementary Table 12), which together identified 23 distinct genes (Supplementary Fig. 6) with significantly different predicted gene expression levels in ADHD cases compared to controls (after Bonferroni correction for all the 34,646 genes and isoforms tested; Supplementary Fig. 6). Eight of the genes were among the 76 genes mapped by credible variants in FUMA. When using a less stringent correction (false discovery rate < 5%), we identified 237 genes with different predicted expression among cases and controls, of which 19 were also among the 76 prioritized risk genes. The *B4GALT2-205* isoform located in the genome-wide significant locus on chromosome 1 showed the strongest association ($P = 7 \times 10^{-11}$), with lower predicted expression in ADHD compared to controls (Supplementary Fig. 7a). The expression model for *B4GALT2-205* implicated four genome-wide significant variants. The second top gene was *PPP1R16A* ($P = 1.4 \times 10^{-8}$), which showed a predicted under-expression in cases compared to controls. The expression model for this gene implicated one genome-wide significant variant (Supplementary Fig. 7b).

Tissue- and cell type-specific expression of ADHD risk genes.

Gene-based association analysis using MAGMA²⁷ identified 45 exome-wide significant genes ($P < 2.72 \times 10^{-6}$ (0.05/18,381 genes)) associated with ADHD (Supplementary Table 13). Gene association results across the entire genome were tested for a relationship with tissue-specific gene expression. This showed that brain-expressed genes, and in particular genes expressed in the cortex, are associated with ADHD (Supplementary Fig. 8). This result was supported by LDSC-SEG³⁰ analysis, showing a significant enrichment in the heritability by variants located in genes specifically expressed in the frontal cortex (Supplementary Table 14).

Next, we examined neuronal cell type-specific gene expression in ADHD using two approaches. First, we tested for enrichment of variants located in cell-specific epigenomic

peaks by intersecting our genetic associations with data from two recent catalogs of the human epigenome that profile major human body cell types³¹ as well as brain-specific cell types³². Here we found enrichment for genes expressed in major brain neuronal cell types, including both excitatory and inhibitory neurons (Supplementary Fig. 9). Second, we performed cell type-specific analyses in FUMA³³ based on single cell RNA-sequencing data. This revealed a significant association ($P=0.005$) between ADHD-associated genes and genes expressed in dopaminergic midbrain neurons (Linnarsson midbrain data³⁴; Supplementary Fig. 10 and Supplementary Table 15).

Convergence of common and rare variant risk.

To test for convergence of risk conferred by common variants and rare protein-truncating variants (rPTVs), we analyzed whole-exome sequencing data from a subset of the iPSYCH cohort consisting of 8,895 ADHD cases and 9,001 controls. We tested three gene sets: (1) the 76 prioritized risk genes identified by positional and functional annotation, (2) the 45 significant genes in the MAGMA analysis, and (3) 18 genes with at least five credible variants located in the coding region (Supplementary Table 16). While there was no indication of increased burden of rPTVs in the first gene set ($P=0.39$, OR = 1.30, s.e. = 0.16), the second gene set showed borderline nominal significant enrichment ($P=0.05$, OR = 1.43, s.e. = 0.18), and the set of genes identified based on credible variants had a significantly increased burden of rPTVs in individuals with ADHD compared to controls ($P=0.015$, OR = 2.19, s.e. = 0.32). For comparison, there was no enrichment in rare synonymous variants in the third gene set ($P=0.59$). When evaluating the 18 genes from the “credible gene set” individually, *SORCS3* was nominally significantly ($P=0.008$; Supplementary Table 16) enriched in rPTVs in ADHD cases when compared to a combined group of iPSYCH controls and gnomAD individuals (non-psychiatric non-Finnish Europeans; $n=58,121$); this suggests that *SORCS3* might be implicated in ADHD both by common and rare deleterious variants.

Genetic overlap of ADHD with other phenotypes.

The genome-wide genetic correlation (r_g) of ADHD with other phenotypes was estimated using published GWASs (258 phenotypes) and GWASs of UK Biobank data (514 phenotypes), available in LDhub³⁵. ADHD showed significant genetic correlation ($P < 2 \times 10^{-4}$) with 56 phenotypes representing domains previously found to have significant genetic correlations with ADHD: cognition (e.g. educational attainment $r_g = -0.55$, s.e. = 0.021), weight/obesity (e.g. body mass index $r_g = 0.27$, s.e. = 0.03), smoking (e.g. smoking initiation $r_g = 0.48$; s.e. = 0.07), sleep (e.g. insomnia $r_g = 0.46$, s.e. = 0.05), reproduction (e.g. age at first birth $r_g = -0.65$, s.e. = 0.03) and longevity (e.g. mother’s age at death $r_g = -0.42$, s.e. = 0.07). When considering other neurodevelopmental and psychiatric disorders, autism spectrum disorder (ASD) ($r_g = 0.42$, s.e. = 0.05), schizophrenia (SCZ) ($r_g = 0.17$, s.e. = 0.03), major depressive disorder (MDD) ($r_g = 0.31$, s.e. = 0.07) and cannabis use disorder (CUD) ($r_g = 0.61$, s.e. = 0.04) were significantly correlated with ADHD (Supplementary Table 17). In UK Biobank data, ADHD demonstrated the strongest genetic correlation with a low overall health rating ($r_g = 0.60$, s.e. = 0.2; Supplementary Table 18).

Furthermore, we applied MiXeR³⁶, which uses univariate and bivariate Gaussian mixture modeling to quantify the actual number of variants that: (1) explain 90% of the SNP heritability of ADHD and (2) overlap between ADHD and other phenotypes representing domains with high genetic correlation with ADHD (psychiatric disorders, smoking behavior, weight, reproduction, and sleep were evaluated). MiXeR considers all variants, i.e., variants with the same and opposite directions of effects. Approximately 7.3K (standard deviation (s.d.) = 324) common variants were found to influence ADHD, which is less than our estimates for SCZ (9.6K; s.d. = 199), MDD (11.7K; s.d. = 345) and ASD (10.3K; s.d. = 1,011), and less than previously reported for bipolar disorder (BD) (8.6K, s.d. = 200)¹⁸.

When considering the number of shared loci as a proportion of the total polygenicity of ADHD, the vast majority of variants influencing ADHD were also estimated to influence the other investigated psychiatric disorders (84%–98%; Fig. 2, Supplementary Fig. 11, and Supplementary Table 19). While the fraction of concordant variants (within the shared part) with ASD and MDD was at the high end (75–76%), it was lower for SCZ (59%). When considering other phenotypes, insomnia demonstrated the smallest overlap with ADHD in terms of actual number of variants (4.5K, s.d. = 1,281; 62% of ADHD variants shared), while almost all variants influencing ADHD also influence educational attainment, age at first birth and smoking (Fig. 2 and Supplementary Table 19). For insomnia and smoking, 83% and 79% of shared variants had concordant directions, respectively, while only 21% and 20% of ADHD risk variants were concordant with educational attainment and age at first birth associated variants, respectively (Supplementary Table 19).

Impact of ADHD polygenic scores on cognitive domains.

Educational attainment is one of the phenotypes with the strongest negative genetic correlation with ADHD, as demonstrated above, and cognitive impairments in ADHD are well described³⁷. To further explore how ADHD risk variants affect specific cognitive domains, we assessed the association of ADHD polygenic scores (PGS) with 15 cognitive measures in the Philadelphia Neurodevelopmental Cohort (PNC)^{38,39}. This cohort is from the greater Philadelphia area and includes individuals, 8–21 years of age, who received medical care at the Children’s Hospital of Philadelphia Network. The subsample of the PNC cohort (v1 release) of 4,973 individuals with European descent was utilized in this study. The Computerized Neurocognitive Battery⁴⁰ was used to assess cognitive performance in the study participants. The battery consists of 14 tests in five domains: executive control, episodic memory, complex cognitive processing, social cognition and sensorimotor speed. Additionally, the Wide Range Achievement Test (WRAT-4)⁴¹ was used as a proxy measure for overall IQ³⁹.

ADHD-PGS was negatively associated with seven neurocognitive measures (Fig. 3), with the strongest association for the WRAT-4 test ($\beta = -0.09$, $P = 1.09 \times 10^{-10}$). ADHD-PGS was associated with measures of executive control (attention: $\beta = -0.08$, $P = 3.94 \times 10^{-8}$; working memory: $\beta = -0.05$, $P = 1.56 \times 10^{-3}$), complex cognition (verbal reasoning: $\beta = -0.08$, $P = 1.31 \times 10^{-10}$; non-verbal reasoning: $\beta = -0.05$, $P = 1.08 \times 10^{-3}$; spatial reasoning: $\beta = -0.06$, $P = 5.15 \times 10^{-5}$) and one measure of episodic memory (facial memory: $\beta = -0.05$, $P = 3.23 \times 10^{-3}$) (Supplementary Table 20). The negative association

of ADHD risk variants with executive functions, especially attention, is in line with the inattention problems often observed in individuals with ADHD.

DISCUSSION

The present study identified 27 genome-wide significant loci in the largest GWAS of ADHD to date. We analyzed around twice as many ADHD cases compared to the ADHD2019¹⁴ study and more than doubled the number of associated loci, indicating that we have passed the inflection point for ADHD with respect to the rate of risk loci discovery.

Six of the 12 previously identified loci were also significant in this study. Even though some previously identified loci demonstrated weaker association here, their associations remained strong, and there was almost complete concordance in the direction of association between top-associated variants in this study and ADHD2019. In GWAS of complex disorders, it is not uncommon for some loci to fluctuate around the significance threshold with increasing sample sizes until they eventually achieve stable significance; this can often be attributed to the “winner’s curse” phenomenon, where effect size estimates close to the discovery threshold tend to be overestimated in initial GWAS⁴².

We report a lower h^2_{SNP} for ADHD ($h^2_{\text{SNP}} = 0.14$) than estimated previously ($h^2_{\text{SNP}} = 0.22$). This is driven by a lower h^2_{SNP} in the PGC and deCODE cohorts compared to iPSYCH. Different ascertainment and diagnostic strategies and designs among PGC cohorts could decrease the h^2_{SNP} , while a lower effective sample size⁴³ in Iceland, and thus fewer recent variants, might bias h^2_{SNP} downwards in the deCODE cohort⁴⁴.

We refined ADHD’s genetic architecture by estimating that around 7.3K (s.d. = 324) common variants can explain 90% of the h^2_{SNP} . This is a higher estimate than reported based on the 2019 ADHD GWAS (5.6K, s.d. = 400)⁴⁵, but the current estimate is based on a better fit to the causal mixture model (AIC = 80 vs. AIC = 31 in Hindley et al.⁴⁵). ADHD is often comorbid with other psychiatric disorders⁴⁶, with 12–16% of cases also diagnosed with ASD^{16,47,48} and around 40% with depression⁴⁹, which is also reflected in the genetic correlations reported here and previously¹⁴. Strikingly, when assessing both concordant and discordant allelic directions, over 90% of ADHD risk variants also seem to influence SCZ and MDD, and 84% influence ASD. This extensive sharing with SCZ, MDD, and ASD is at the same level as observed for SCZ and bipolar disorder³⁶, which are among the most genetically correlated mental disorders⁵⁰. Notably, for both MDD and ASD, around 75% of the variants shared with ADHD demonstrated concordant direction of association. The large sharing of variants influencing ADHD and other psychiatric disorders, when assessing both concordant and discordant allelic directions, suggests that the disorders are even more intermingled with respect to their common genetic architecture than previously thought based on their overall genetic correlations^{36,50}. For common variants, the developmental trajectory towards ADHD might therefore be influenced by variants involved in several psychiatric disorders, but with disorder-specific allelic directions and effect sizes rather than actual ADHD-specific loci.

We also note that almost all variants that influence ADHD overlap with educational attainment⁵¹, and that the vast majority (79%) are associated with decreased educational attainment, consistent with the overall negative genetic correlation. For the models indicating a high number of shared variants (ADHD vs. MDD, SCZ, BMI, educational attainment, age at first birth and smoking), we found support (evaluated using the Akaike Information Criterion⁵²) for the best fitting MiXeR models above the “minimal model”, which indicate that the data support the existence of a polygenic overlap, beyond the minimal level needed to explain the observed genetic correlations. For ADHD vs. ASD, the model had limited support, and the results should therefore be interpreted with caution.

Fine-mapping of the 27 loci identified credible variants, but only four variants had posterior probabilities greater than 0.5 in all three fine-mapping methods, and none were linked to specific genes based on our functional annotation analyses. Linking the credible variants to genes by integration with functional genomics data identified 76 prioritized risk genes, which were enriched among genes upregulated during early embryonic development and involved in cognitive abilities identified by GWAS of cognitive phenotypes. Among the 76 genes were *PPP1R16A* and *B4GALT2* (mapped by psychENCODE eQTLs; Supplementary Fig. 12a,b), which were also the top-ranking genes in our TWAS of DLPFC expression, both showing a predicted decreased expression in cases compared to controls. These genes have not previously been linked to psychiatric disorders, but both have been linked to educational attainment⁵¹. The set of risk genes also included *PTPRF*, *SORCS3* and *DCC*, which encode integral components of the postsynaptic density membrane. Involvement of postsynaptic components in the pathology of ADHD has been reported previously⁵³ and also for SCZ⁵⁴. We also highlight *FOXP1* and *FOXP2*. The association signals were located within the transcribed regions of both genes and had credible variants being eQTLs (*FOXP2*, Supplementary Fig. 12c) or located in chromatin interacting regions (*FOXP1*, Supplementary Fig. 12d) in brain tissue. *FOXP2* was identified in the ADHD2019 study¹⁴ and is also a risk gene for cannabis use disorder⁵⁵, while *FOXP1* is a new ADHD locus. Both *FOXP1* and *FOXP2* encode transcription factors that can heterodimerize to regulate transcription in brain tissues^{56,57} and have been implicated in speech disorders and intellectual disability⁵⁸ by highly penetrant rare variants.

Overall, less than half of the TWAS Bonferroni significant genes overlapped with the 76 candidate risk genes (40% of “TWAS transcript genes”; and 47% of “TWAS genes”; Supplementary Fig. 13). This was not unexpected and could be due to noise in the data and/or that TWAS models are based on expression in adult brains whereas a large proportion of individuals in the GWAS are children. Additionally, eQTLs used to derive TWAS models might not overlap GWAS identified variants as the two types of methods are systematically biased toward identification of different types of variants⁵⁹.

We report convergence of common and rare variants in a set of 18 genes defined by location of credible variants. Thirteen of the genes were hit by rPTVs, and eight had a higher load in cases compared to controls, and thus, the signal was not driven by a few genes but by several genes with an increased burden of rPTVs. Of particular note, *SORCS3* seems to be implicated in ADHD by both common and rare variants. Common variants in *SORCS3* show strong pleiotropic effects across several major psychiatric disorders⁵⁰, but to our knowledge,

rare variant analyses have not implicated *SORCS3* in psychiatric disorders before. Our results add to the emerging picture of overlap between genes and pathways affected by common and rare variants in psychiatric disorders^{54,60–62}.

We found that ADHD risk was associated with common variants located in genes significantly expressed in the brain, especially the frontal cortex. We also observed an enrichment of ADHD risk variants in genes expressed in major cell types of the brain, including both excitatory and inhibitory neurons and in midbrain dopaminergic neurons. The findings for frontal cortex and dopamine neurons fit well with the motor, reward and executive function deficits associated with ADHD; the frontal cortex is involved in executive functions including attention and working memory⁶³, and midbrain dopaminergic neurons are essential for controlling key functions, such as voluntary movement⁶⁴ and reward processing⁶⁵. This interpretation is further supported by our ADHD-PGS analyses in PNC, which revealed that common ADHD risk variants impair several domains of cognitive abilities.

The PGS analyses in PNC identified strong association of polygenic ADHD risk with decreased overall IQ (approximated by the WRAT test scores), in line with the high negative genetic correlation of ADHD with educational attainment and the observation that 79% of all ADHD risk variants are associated with decreased educational attainment. Interestingly, we found that ADHD-PGS associates with decreased attention, which is a key ADHD symptom, and with impairments in measures of other cognitive traits such as working memory. Smaller studies have analyzed the impact of ADHD-PGS on executive functions with mixed results^{66–69}. This study robustly identifies specific cognitive domains impacted by ADHD-PGS, and our results support ADHD-PGS being negatively associated with neurocognitive performance.

In summary, we identified new ADHD risk loci, highlighted candidate causal genes, and implicated genes expressed in frontal cortex and several brain specific neuronal subtypes in ADHD. Our analyses revealed ADHD to be highly polygenic, influenced by thousands of variants, of which the vast majority also influence other psychiatric disorders with concordant or discordant effects. Additionally, we demonstrated that common variant ADHD risk has an impairing impact on a range of executive functions. Overall, the results advance our understanding of the underlying biology of ADHD and reveal novel aspects of ADHD's polygenic architecture, its relationship with other phenotypes, and its impact on cognitive domains.

METHODS

The study was approved by the local scientific ethics committees and IRBs. The iPSYCH study was approved by the Scientific Ethics Committee in the Central Denmark Region (Case No 1-10-72-287-12) and the Danish Data Protection Agency. In accordance with Danish legislation, the Danish Scientific Ethics Committee has, for this study, waived the need for specific informed consent in biomedical research based on existing biobanks. This deCODE study was approved by the National Bioethics Committee of Iceland (VSN 15-047) and all participants gave informed consent.

Samples, quality control and imputation.

iPSYCH.—The iPSYCH^{15,70} cohort consists of 129,950 genotyped individuals, among which 85,891 are cases diagnosed with at least one of six mental disorders (i.e., ADHD, SCZ, BD, MDD, ASD, post-partum disorder) and the remaining are population-based controls. Samples were selected from a baseline birth cohort comprising all singletons born in Denmark between May 1, 1981, and December 31, 2008, who were residents in Denmark on their first birthday and who have a known mother ($n = 1,657,449$). ADHD cases were diagnosed by psychiatrists according to the ICD10 criteria (F90.0, F90.1, F98.8 diagnosis codes) identified using the Danish Psychiatric Central Research Register⁷¹ and the Danish National Patient register⁷². Diagnoses were given in 2016 or earlier for individuals at least 1 year old. Controls were randomly selected from the same nationwide birth cohort and not diagnosed with ADHD.

Detailed information on genotyping, imputation and quality control can be found in the Supplementary Note. After QC, the iPSYCH1 ADHD sample included 38,899 individuals and iPSYCH2 included 24,144 individuals.

deCODE.—The deCODE cohort consisted of 8,281 individuals with ADHD. These were either individuals with a clinical diagnosis of ADHD ($n = 5,583$) according to the ICD10 criteria (ICD10-F90, F90.1, F98.8) or individuals that have been prescribed medication specific for ADHD symptoms (ATC-NA06BA, mostly methylphenidate) ($n = 2,698$). The control sample did not contain individuals with a diagnosis of SCZ, BD, ASD or self-reported ADHD symptoms or diagnosis. All participants who donated samples gave informed consent. Information about genotyping, QC and evaluation of potential genetic heterogeneity between individuals identified based on diagnosis codes and medication can be found in the Supplementary Note.

PGC cohorts.—We used summary statistics from the 10 PGC cohorts with European ancestry generated as a part of our previous GWAS meta-analysis of ADHD. Detailed information about cohort design, genotyping, QC, and imputation can be found in Demontis et al.¹⁴.

GWAS meta-analysis of ADHD.

GWASs were performed separately for iPSYCH1 (17,019 cases and 21,880 controls) and iPSYCH2 (8,876 cases and 15,268 controls) using dosages for imputed genotypes and additive logistic regression with the first 10 PCs (from the final PCAs) as covariates using PLINK v1.9.

GWAS of deCODE samples (8,281 ADHD cases; 137,993 controls) was done using dosage data and logistic regression with sex, year of birth, and county of origin as covariates. To account for inflation due to population stratification and cryptic relatedness, test statistics were divided by an inflation factor ($\lambda = 1.23$) estimated from LD score regression as done previously⁵⁵. Findings from analyses of the genetic structure of the Icelandic population by Price et al.⁷³ support that lambda correction will ensure proper correction without false positives. Subsequently alleles were converted to match HRC alleles.

For the PGC cohorts, we used GWAS summary statistics for each of the 10 European PGC cohorts generated as a part of our previous GWAS meta-analysis¹⁴.

See Supplementary Note for sensitivity analyses related to the impact of using sex and age as covariates in the analyses. See Supplementary Figure 14 for the impact of including or excluding sex as covariate in GWAS of iPSYCH data.

Summary statistics from GWAS of the individual cohorts, containing variants with imputation quality (INFO score) > 0.8 and minor allele frequency > 0.01, were meta-analyzed with a fixed effects standard error weighted meta-analysis using METAL (version 2011-03-25)⁷⁴. Only variants supported by an effective sample size greater than 60% were retained in the final summary statistics (6,774,224 variants).

Concordance in the direction of associations in the present GWAS with associations in the ADHD2019 data was evaluated by a sign-test at different *P*-value thresholds (see thresholds in Supplementary Table 4).

Conditional analysis.

We identified potentially independent genome-wide significant lead variants for four loci located on chromosome 1 (two secondary lead variants), 5, 11 and 20. To evaluate if these variants were independent from the lead variants, we performed association analyses of the secondary variants while conditioning on the index variant in the locus using COJO as implemented in GCTA²¹.

Identification of sets of credible variants.

To identify sets of causal variants, we fine-mapped each of the 27 genome-wide loci using three fine-mapping tools, FINEMAP v. 1.3.1 (ref. ⁷⁵), PAINTOR v.3.0 (ref. ⁷⁶) and CAVIARBF v.0.2.1 (ref. ⁷⁷), using CAUSALdb-finemapping-pip downloaded from <https://github.com/mulinlab/CAUSALdb-finemapping-pip>⁷⁸. Since no secondary lead variants remained genome-wide significant after conditional analyses, one causal variant was assumed per locus. Variants located in a region of 1 Mb around index variants were included in the analyses. We used a threshold of 95% for the total posterior probability of the variants included in the credible sets, and only variants claimed to be within the set by all three methods were included in the final credible set for each locus.

Genetic correlations among cohorts and SNP heritability.

SNP heritability (h^2_{SNP}) and pair-wise genetic correlation among the cohorts were calculated using LD score regression⁷⁹ analysis of summary statistics from GWAS of deCODE samples, meta-analysis of iPSYCH1+iPSYCH2 and meta-analysis of the 10 PGC cohorts (applying the same approach as described for the meta-analysis of all cohorts). Conversion of h^2_{SNP} estimates from observed scale to the liability scale was done using a population prevalence of 5%. Test for significant differences in h^2_{SNP} between cohorts was done using a *Z*-test.

Mapping of risk genes, enrichment and pathway analyses.

To link identified risk variants to genes, we used the set of credible variants (identified as described above) for each locus and linked variants to genes based on genomic position and functional annotations in FUMA²³. Protein coding genes were mapped if they were located with a distance of 10 kb upstream or downstream of the index variants or if a credible variant was annotated to the gene based on eQTL data or chromatin interaction data from human brain (datasets used are listed in the Supplementary Note). The mapping linked credible variants to 76 ADHD prioritized risk genes. These genes were used in gene-set enrichment analyses to evaluate if the candidate genes were enriched among (1) genes differentially expressed in specific brain tissues, (2) genes differentially expressed at specific brain developmental stages, (3) genes encoding proteins involved in synapses and (4) genes encoding proteins in specific biological pathways. We corrected for multiple testing separately for each of these hypotheses. The first two aims were addressed by performing enrichment analyses in the GENE2FUNC module in FUMA. Enrichment of ADHD risk genes among predefined sets of differentially expressed genes in GTEx (54 tissue types) and BrainSpan (29 different ages of samples and 11 general developmental stages) data using hypergeometric test, and protein-coding genes were chosen as background genes.

The third aim was addressed using SynGO²⁴ (dataset version: 20210225) to test for enrichment among the 76 risk genes for genes involved in synaptic processes and locations. We analyzed for enrichment in two subsets: “biological process” (201 gene sets) and “cellular component” (92 gene sets). We controlled using a background set of “brain expressed” genes provided by the SynGo platform (defined as ‘expressed in any GTEx v7 brain tissues’) containing 18,035 unique genes, of which 1,225 overlap with SynGO annotated genes. For each ontology term, a one-sided Fisher exact test was performed to compare the list of ADHD risk genes and the selected background set. To find enriched terms within the entire SynGO ontology, the most specific term is selected where each ‘gene cluster’ (unique set of genes) is found and then multiple testing correction is applied using False Discovery Rate (FDR) on the subset of terms that contain these ‘gene clusters’. Only ontology terms with gene sets with a minimum of three genes were included in the enrichment analysis.

The fourth aim was addressed by testing if the 76 genes were enriched in pathways/gene sets using Enrichr^{25,26} and its implemented databases (26 databases). Only pathways enriched with more than two genes were considered. We took a conservative approach and only considered pathways to be significant if the within-database adjusted *P*-value was smaller than 0.002 (0.05/26 databases evaluated). After correction for the number of databases, no significantly enriched pathways were identified.

We also tested for enrichment among the 76 genes of genes reported from the GWAS catalog (2019) and UK Biobank GWASs (v1) and used https://appymatters.maayanlab.cloud/Enrichr_Manhattan_Plot/ to visualize the results.

Finally, we conducted pathway enrichment analysis using results from the full GWAS meta-analysis (i.e., no preselection of genes) by performing MAGMA²⁷ gene-set analysis in FUMA (see details in the Supplementary Note).

Transcriptomic imputation model construction and TWAS.

Transcriptomic imputation models were constructed as previously described²⁸ for dorso-lateral prefrontal cortex (DLPFC) transcript levels⁸⁰. The genetic dataset of the PsychENCODE cohort was uniformly processed for quality control (QC) steps before genotype imputation. The analysis was restricted to samples with European ancestry as previously described²⁸. Genotypes were imputed using the University of Michigan server⁸¹ with the Haplotype Reference Consortium (HRC) reference panel⁸². Gene expression information (both at the level of gene and transcript) was derived from RNA-seq counts which were adjusted for known and hidden confounds, followed by quantile normalization⁸⁰. For the construction of the transcriptomic imputation models, we used EpiXcan²⁸, an elastic net-based method, which weighs SNPs based on available epigenetic annotation information⁸³. We performed the transcript-trait association analysis for ADHD as previously described²⁸. Briefly, we applied the S-PrediXcan method²⁸ to integrate the ADHD GWAS meta-analysis summary statistics and the transcriptomic imputation models constructed above to obtain association results at both the level of genes and transcripts.

Gene-based association and tissue-specific gene expression.

We used MAGMA v1.08 implemented in FUMA v1.3.6a²³ to perform gene-based association analysis using the full summary statistics from the GWAS meta-analysis. Genome-wide significance was assessed through Bonferroni correction for the number of genes tested ($P = 0.05/18381 = 2.72 \times 10^{-6}$).

The relationships between tissue-specific gene expression profiles and ADHD-gene associations were tested using MAGMA gene-property analysis of expression data from GTEx (54 tissue types) and BrainSpan (29 brain samples at different ages) available in FUMA (see Supplementary Note for datasets selected).

Enrichment in h^2_{SNP} of ADHD-associated variants located in or close to genes expressed in specific brain regions was estimated using LDSC-SEG³⁰. Annotations indicating specific expression in 13 brain regions from the GTEx gene expression database were downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/LDSC_SEG_ldscores/.

Cell type-specific expression of ADHD risk genes.

We tested for enrichment in the ADHD h^2_{SNP} of variants located in cell type-specific epigenetic peaks by examining the overlap of common genetic risk variants with open chromatin from a DHS (DNase I hypersensitive sites) study profiling major human cell types³¹ and an scATAC-seq (single-cell assay for transposase accessible chromatin)³² study using an LD-score partitioned heritability approach⁸⁴. All regions of open chromatin were extended by 500 bp in either direction. The broad MHC region (hg19 chr6:25–35Mb) was excluded due to its extensive and complex LD structure, but otherwise default parameters

were used for the algorithm. We applied Bonferroni correction (correcting for 23 cell types), and results below $P = 0.0022$ were considered significant.

Additionally, we performed cell type-specific analyses implemented in FUMA, using data from 13 single-cell RNA sequencing datasets from human brain. The method is described in detail in Watanabe et al.³³. Datasets used and a short summary of the method can be found in the Supplementary Note).

Overlap of common ADHD risk variants with rare protein-truncating variants (rPTVs).

We analyzed the overlap of common variants with rPTVs in a subset of iPSYCH samples that have also been whole exome sequenced. A major part of the data (Pilot 1, Wave 1, Wave 2) was also included in the recent study by Satterstrom et al.¹⁷, and the same quality control procedure was applied in this study. Description of whole-exome sequencing procedure, QC and annotation can be found in the Supplementary Note. Variants were defined as PTVs if they were annotated as having large effects on gene function (nonsense variant, frameshift, splice site). We defined a variant as being rare if it had an allele count of five or less across the combination of the full iPSYCH exome-sequencing dataset ($n = 28,448$) and non-Finnish Europeans in the nonpsychiatric gnomAD exome database ($n = 44,779$).

We tested for increased burden of rPTVs in ADHD compared to controls in three gene sets: (1) the 76 genes linked to credible variants based on position and functional genomic data, (2) the 45 exome-wide significant genes identified in MAGMA analysis, and (3) genes with at least five credible variants within the coding regions. The requirement of five credible variants was chosen to prioritize the most likely causal genes. This threshold excluded eight genes located in the same locus covering a broad LD region on chromosome 3 (Supplementary Data 1; page 25). Additionally, two other genes with less than five credible variants were excluded located in two other loci on chromosome 3.

The burden of rPTVs and rare synonymous (rSYNs) in cases compared to controls was tested for the three gene sets with logistic regression corrected using the following covariates: birth year, sex, first ten principal components, number of rSYN, percentage of target with coverage $> 20x$, mean read depth at sites within the exome target passing VQSR, total number of variants, sequencing wave.

Only significant enrichment in the set of 18 genes identified based on credible variants was found. We therefore looked specifically into these genes to identify whether the signal was driven by specific genes. rPTVs were found in 13 of the genes, and eight of these genes had more rPTVs in cases than controls when looking at raw counts (Supplementary Table 16). We performed gene-based burden test using EPACTS (<https://genome.sph.umich.edu/wiki/EPACTS>) and a logistic Wald test (correcting using the covariates as described above). Additionally, in order to increase power to detect an increased burden of rPTVs at the gene level in ADHD cases, we combined iPSYCH controls with information about rPTVs in gnomAD (non-Finnish European individuals), done as described previously¹⁷. We performed these gene-based tests using Fisher's exact test, and only the following genes were considered: (1) genes with a higher number rSYN in gnomAD controls compared to

iPSYCH cases, and (2) genes with a higher rate of rPTVs in cases compared to controls in the iPSYCH data.

Genetic overlap with other phenotypes.

We estimated genetic correlations of ADHD with other phenotypes in LDhub³⁵ (published GWASs: 255 phenotypes; UK Biobank GWASs: 514 phenotypes). Additionally, genetic correlations with three phenotypes not available in LDhub (cannabis use disorder⁵⁵, smoking initiation⁸⁵ and education attainment⁵¹) were estimated locally using LD score regression⁷⁹.

We applied MiXeR³⁶ to our ADHD GWAS summary statistics and GWAS from a selection of complex traits showing high genetic correlation with ADHD: ASD⁸⁶, SCZ⁵⁴, BMI⁸⁷, educational attainment⁸⁸, age at first birth⁸⁹, smoking initiation⁸⁵, insomnia⁹⁰ and a new GWAS meta-analysis of depression including 371,184 cases and 978,703 controls⁹¹ (Supplementary Table 19) to quantify (i) the number of variants influencing each trait and (ii) the genetic overlap between ADHD and each of the other traits. We used MiXeR with default settings (<https://github.com/precimed/mixer>) in a two-step process. First, we ran a univariate model for each trait to estimate the number of common variants having a non-zero genetic additive impact on the phenotype. The univariate model generates estimates of “polygenicity” (i.e., the proportion of non-null variants) and “discoverability” (i.e., the variance of effect sizes of non-null SNPs). Second, the variance estimates from the univariate step were used to run a bivariate model in a pairwise fashion (i.e. ADHD vs. each of the other traits), which produced estimates of SNPs with a specific effect on the first or on the second trait, and SNPs with a non-zero effect on both traits (for details on the method see also ref. 18 and Supplementary Note). The models were evaluated by the Akaike Information Criterion⁵² (AIC) and illustrated with modeled versus observed conditional quantile-quantile (Q-Q) plots (Supplementary Fig. 11). The AIC values can be found in Supplementary Table 19.

Polygenic score (PGS) analysis of cognitive measures in PNC.

PGS analysis was performed on 4,973 individuals of European ancestry from the Philadelphia Neurodevelopmental Cohort (PNC), ages 8–21. Information about imputation and QC of the PNC data can be found in the Supplementary Note.

The software PRS-CS⁹² was used to process ADHD GWAS summary statistics and assign per-allele posterior SNP effect sizes. A European LD reference panel generated from the 1000 Genomes Project data (<https://github.com/getian107/PRS-CS>) was utilized. The following default settings were used for PRS-CS: parameter a in the γ - γ prior = 1, parameter b in the γ - γ prior = 0.5, MCMC iterations = 1000, number of burn-in iterations = 500, and thinning of the Markov chain factor = 5. Additionally, the global shrinkage parameter ϕ was determined using a fully Bayesian method. Plink v2.0⁹³ was then used to calculate individual-level ADHD PGS. Linear regression was used to test the association between ADHD PGS and neurocognitive phenotypes measured in the PNC. Age (at time of neurocognitive testing), age², genotyping batch, sex, and the first 10 MDS dimensions were used as covariates. The neurocognitive measures were obtained using the Computerized Neurocognitive Battery (CNB), which consists of 14 tests in 5 domains: executive control,

episodic memory, complex cognitive processing, social cognition, and sensorimotor speed. The battery has been described in detail elsewhere⁴⁰. Additionally, association of ADHD-PGS with results from the Wide Range Achievement Test (WRAT-4)⁴¹ were analyzed. See Supplementary Note regarding transformation of the CNB measures.

The total variance explained by ADHD-PGS and model covariates for each neurocognitive phenotype was reported using Adjusted R². Additionally, the variance explained by ADHD-PGS was calculated in R using a variance partitioning tool (https://github.com/GabrielHoffman/misc_vp/blob/master/calcVarPart.R). Reported *P*-values were Bonferroni-adjusted to account for the number of independent tests performed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Summary statistics from the ADHD GWAS meta-analysis are available for download at the PGC website (<https://www.med.unc.edu/pgc/download-results/>). All relevant iPSYCH data are available from the authors after approval by the iPSYCH Data Access Committee and can only be accessed on the secured Danish server (GenomeDK; <https://>

genome.au.dk) as the data are protected by Danish legislation. For data access and correspondence, please contact Ditte Demontis (ditte@biomed.au.dk) or Anders D. Børglum (anders@biomed.au.dk).

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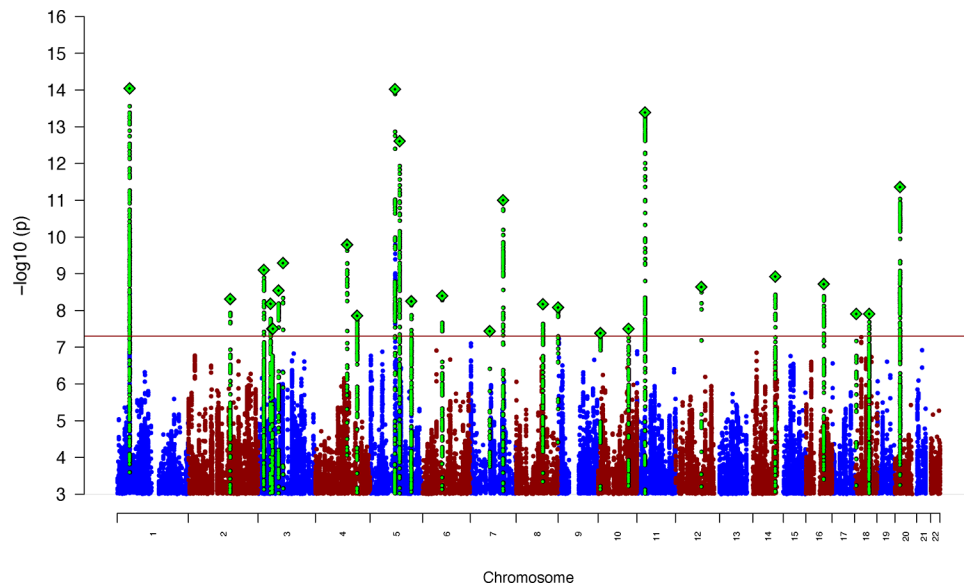


Figure 1 | Results from GWAS meta-analysis of iPSYCH, deCODE and PGC cohorts including 38,899 cases and 186,843 controls in total.

The y -axis represents $-\log_{10}(\text{two-sided } P\text{-values})$ from meta-analysis using an inverse-variance weighted fixed effects model. Index variants in each of the genome-wide significant loci are marked as a green diamond (note that two loci on chromosome 3, index variants rs7613360 and rs2311059, are located in close proximity and therefore appear as one diamond in the plot). The red horizontal line represents the threshold for genome-wide significant association ($P = 5 \times 10^{-8}$).

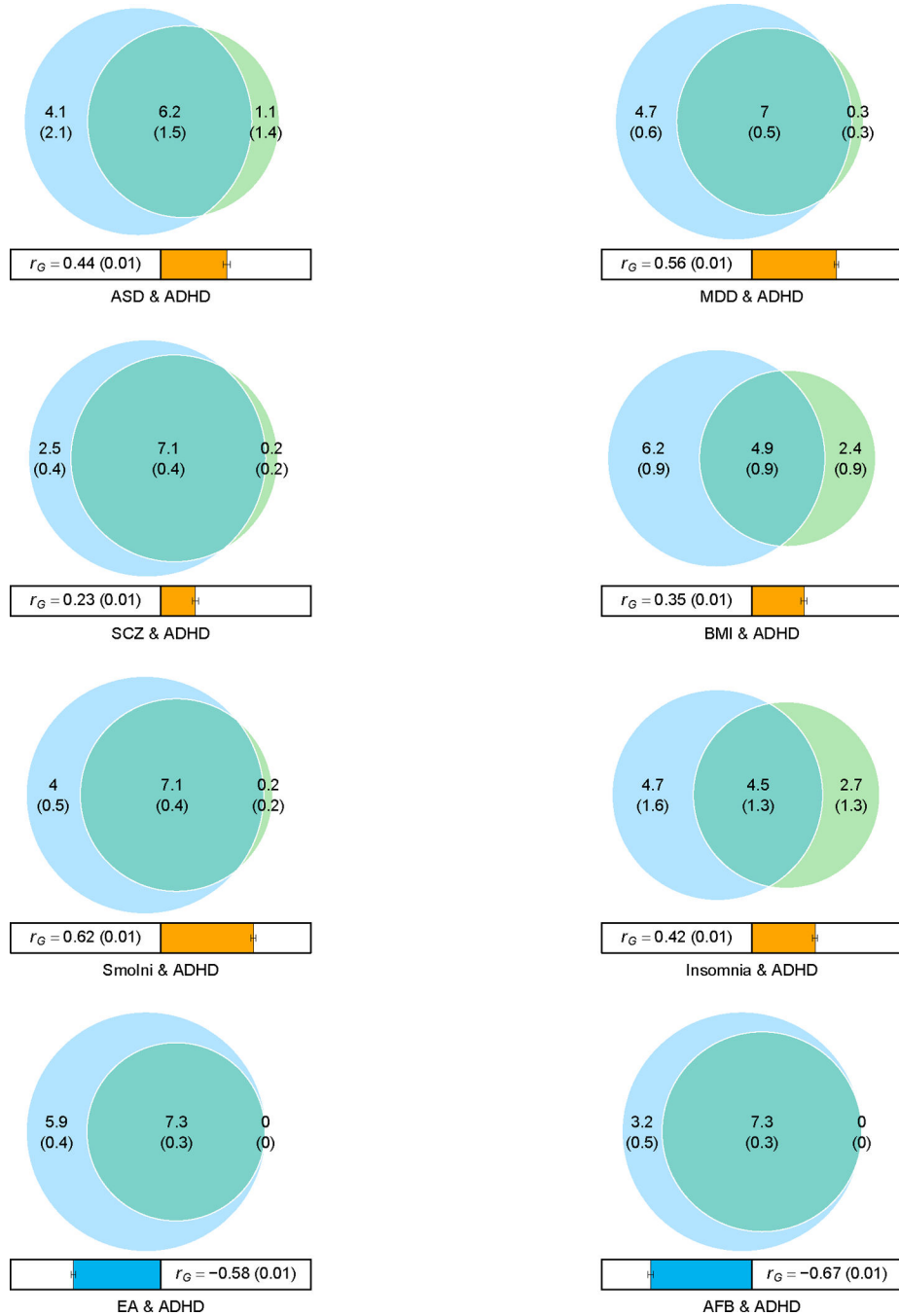


Figure 2 | Venn diagrams showing MiXeR results of the estimated number of variants shared between ADHD and psychiatric disorders (with significant genetic correlations with ADHD) and phenotypes representing other domains with high genetic correlation with ADHD.

Circles represent shared variants (gray), unique to ADHD (light blue) and unique to the other phenotype of interest (orange). The number of shared variants (and standard deviations) is shown in thousands. The size of the circles reflects the polygenicity of each phenotype, with larger circles corresponding to greater polygenicity. The estimated genetic correlation (r_G) between ADHD and each phenotype from LDSC is shown below the corresponding Venn diagram, with an accompanying scale (-1 to +1) with blue

and red representing negative and positive genetic correlations, respectively. Bivariate results for ADHD, autism spectrum disorder (ASD), major depressive disorder (MDD), schizophrenia (SCZ), body mass index (BMI), smoking initiation (SmoIni), insomnia, educational attainment (EA) and age at first birth (AFB) are shown (see also Supplementary Table 17).

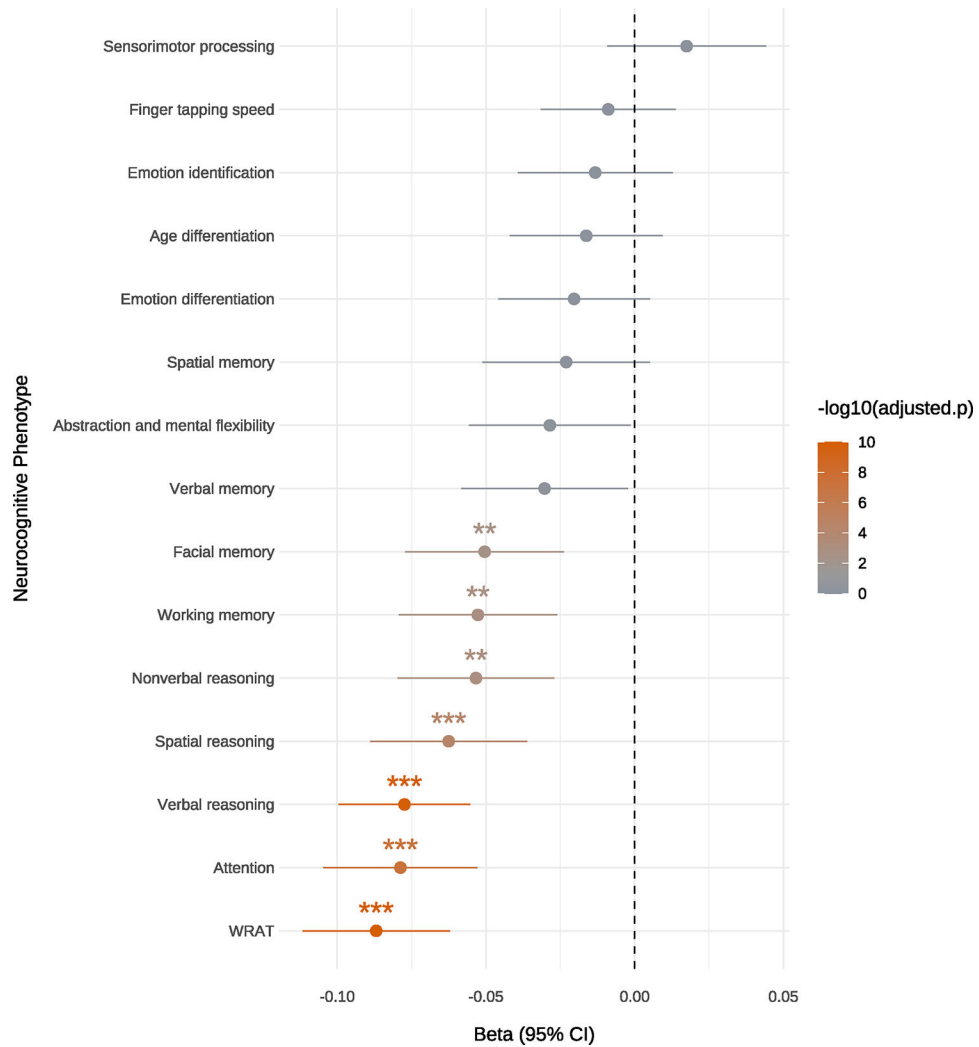


Figure 3 | Association of ADHD-PGS with measures of cognitive abilities in the PNC cohort ($n = 4,973$).

Beta values (represented as a dot and standard errors indicated as horizontal bars) from linear regression testing for the association of ADHD-PGS with the 15 neurocognitive measures listed on the y -axis (Wide Range Achievement Test-4 (WRAT)). The color bar at the right indicates the $-\log_{10}(\text{Bonferroni adjusted two-sided } P\text{-value})$ and P -value thresholds are indicated by stars (* $P=0.05$; ** $P=0.01$, *** $P=0.001$).

Table 1 |
Results for the 27 genome-wide significant index variants identified in the GWAS meta-analysis of 38,691 individuals with ADHD and 186,843 controls.

The location (chromosome (chr)) base position (bp) in hg19), alleles (A1 and A2), frequency (Freq.) of A1 in cases and controls, odds ratio (OR) of the effect with respect to A1, standard error (s.e.) and association *P*-values (two-sided) from inverse-variance weighted fixed effects model of the index variants are given. “Novel” indicates if the locus is a new ADHD risk locus i.e., not identified in ADHD2019 (ref. ¹⁴). Nearby genes located within 50 kb from index variants are listed (for a list of mapped genes based on other criteria see Supplementary Table 8).

Genomic locus	chr	bp	rs ID	A1	A2	Nearby genes	Freq. cases	Freq. controls	OR	s.e.	<i>P</i> -value	Novel
	1	44076469	rs549845	G	A	<i>PTPRF, KDM4A</i>	0.321	0.326	1.082	0.01	9.03E-15	no
	2	145714354	rs1438898	A	C		0.762	0.769	1.065	0.01	4.88E-09	yes
	3	20724204	rs2886697	G	A		0.634	0.643	1.061	0.01	7.90E-10	no
	4	43691501	rs9877066	G	A	<i>SNRK, ANO10, ABHD5</i>	0.944	0.951	0.888	0.02	6.60E-09	yes
	5	49916710	rs7613360	C	T	<i>TRAI, CAMKV, MST1R, CTD-2330K9.3, MON1A</i>	0.598	0.614	0.948	0.01	3.18E-08	yes
	6	51884072	rs2311059	G	A	<i>IQCF3, IQCF2, IQCF5, IQCF1</i>	0.314	0.308	0.944	0.01	3.16E-08	yes
	7	71499401	rs17718444	C	T	<i>FOXP1</i>	0.695	0.660	1.063	0.01	2.87E-09	yes
	8	87015142	rs114142727	C	G	<i>VGLL3</i>	0.988	0.988	1.285	0.04	5.13E-10	yes
	9	112217523	rs17576773	C	T		0.888	0.880	1.101	0.02	1.63E-10	yes
	10	147099654	rs6537401	G	A	<i>LSM6, RP11-6L6.2, SLC10A7</i>	0.660	0.655	0.945	0.01	1.40E-08	yes
	11	87854395	rs4916723	A	C		0.553	0.573	0.918	0.01	9.48E-15	no
	12	103964585	rs77960	G	A		0.665	0.682	0.929	0.01	2.46E-13	yes
	13	144474779	rs10875612	C	T		0.483	0.470	0.947	0.01	5.62E-09	yes
	14	70858701	rs2025286	A	C	<i>COL19A1</i>	0.553	0.550	0.947	0.01	4.00E-09	yes
	15	67685754	rs73145587	A	T		0.910	0.901	1.107	0.02	3.67E-08	yes
	16	114158954	rs9969232	G	A	<i>FOXP2</i>	0.344	0.382	0.934	0.01	9.98E-12	no
	17	93277087	rs7844069	T	G		0.428	0.399	1.057	0.01	6.74E-09	yes
	18	145802447	rs4925811	T	G	<i>C8orf82, ARHGAP39</i>	0.515	0.531	0.944	0.01	8.30E-09	yes
	19	8784773	rs11255890	C	A		0.389	0.401	1.054	0.01	4.14E-08	yes
	20	106453832	rs11596214	G	A	<i>SORCS3</i>	0.597	0.569	1.054	0.01	3.17E-08	no
	21	28602173	rs2582895	C	A	<i>METTL15</i>	0.634	0.618	1.075	0.01	4.09E-14	yes
	22	89771903	rs704061	T	C	<i>DUSP6, POC1B</i>	0.554	0.560	0.946	0.01	2.30E-09	no
	23	98690923	rs76284431	T	A		0.847	0.842	0.922	0.01	1.19E-09	yes
	24	61966703	rs1162202	C	T	<i>CDH8</i>	0.630	0.606	1.063	0.01	1.92E-09	yes
	25	5871800	rs76857496	C	A	<i>TMEM200C</i>	0.870	0.859	1.083	0.01	1.24E-08	yes
	26	50625779	rs7506904	G	A	<i>DCC</i>	0.343	0.372	0.946	0.01	1.24E-08	yes

Genomic locus	chr	bp	rs ID	A1	A2	Nearby genes	Freq. cases	Freq. controls	OR	s.e.	P-value	Novel	
	27	20	21250843	rs6082363	T	C	<i>XRN2, NKX2-4</i>	0.296	0.291	1.073	0.01	4.38E-12	yes

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