Online supplement for Klein et al., Genetic Markers of ADHD-Related Variations in Intracranial Volume. Am J Psychiatry (doi: 10.1176/appi.ajp.2018.18020149)

SUPPLEMENTARY MATERIAL: Supplementary methods, figures, and tables

SUPPLEMENTARY METHODS

Participant samples

ADHD Working Group of the PGC and the ADHD iPSYCH-SSI-Broad collaboration

ADHD GWAS-MA summary statistics data were acquired from the ADHD Working Group of the PGC and the ADHD iPSYCH-SSI-Broad collaboration (n=55,374 (1), https://www.med.unc.edu/pgc/results-and-downloads). Detailed quality control and imputation parameters are described in the original publication (1). Briefly, genotype imputation was done using the bioinformatic pipeline "ricopili" and with the pre-phasing/imputation stepwise approach implemented in IMPUTE2/SHAPEIT using the haplotypes from the 1000 Genomes Project, phase 3, version 5 (1KGP3v5) (2) data. Association analyses using the imputed marker dosages were performed separately for the 11 PGC samples and the 23 waves in iPSYCH by an additive logistic regression model using PLINK v1.9 (3), with the derived principal components included as covariates as described in the original publication (1). Subsequently, meta-analysis, including summary statistics from GWASs of the 23 waves in iPSYCH and 11 PGC samples, was conducted using an inverse-weighted fixed effects model. In total, 20,183 cases and 35,191 controls were used for the original analysis (**Table S1**). Only SNPs with imputation quality (INFO score) >0.8 and MAF >0.01 were included in the meta-analysis. PGC+iPSYCH ADHD GWAS-MA summary statistics data only included markers which were supported by an effective sample size greater than 70% (8,047,420 markers) (1).

ENIGMA

GWAS-MA summary statistics data on ICV and volumes of nucleus accumbens, amygdala, caudate nucleus, hippocampus, and putamen were from ENIGMA (http://enigma.ini.usc.edu/) (4). In the GWAS-MAs on subcortical volumes those volumes had been adjusted for ICV to identify specific genetic contributions to individual volumes. The five subcortical volumes indicated and ICV were selected for the current study based on a recent mega-analysis reporting significant volume reductions in patients with ADHD compared to healthy controls (5). Access to the summary statistics of ENIGMA can be requested via their website (http://enigma.ini.usc.edu/download-enigma-gwas-results/). For the initial GWAS-MA analysis, MRI brain scans and genome-wide genotype data were available for 11,840 subjects from 22 cohorts. Genomic data were imputed to a reference panel (1000 Genomes, phase1, v3 (1KGP1v3) (6)) comprising only European samples and with monomorphic SNPs removed. Imputation was performed at each site using MaCH for phasing and minimac for imputation (7). Only SNPs with an imputation score of RSQ >0.5 and minor allele counts >10 within each site were included. Tests of association were conducted separately for eight MRI volumetric phenotypes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, thalamus and ICV) with the following covariates in a multiple linear regression framework: age, age2, sex, four MDS components (to account for population structure) and ICV (for subcortical brain phenotypes). GWA statistics from each of the 22 sites were combined using a fixed-effect inverse variance-weighted meta-analysis as implemented in METAL (8). Prior to all analyses, a cohort including ADHD cases (NeuroIMAGE cohort, n=154) was removed from the ENIGMA data.

CHARGE

We obtained genome-wide GWAS-MA summary statistics data on ICV and hippocampal volume from the CHARGE Consortium (n=12,803 and n=13,039, respectively (9, 10)) and CHARGE summary statistics

data had been requested by the principal investigator of the study described by Adams et al. (9). Genotyping was performed using a variety of arrays across contributing sites. Samples and variants underwent quality control procedures based on genetic homogeneity, call rate (< 95%), MAF <0.01, and Hardy-Weinberg Equilibrium (HWE p-value <1×10−6). Good quality variants were used as input for imputation to the 1000 Genomes reference panel (1KGP1v3; (6)) using different software packages (MaCH/minimac, IMPUTE2, BEAGLE, GenABLE). Only SNPs with an imputation score of RSQ >0.5 and MAF>0.5% within each site were included in the meta-analysis. Full details on the site-specific genotyping and quality control can be found in Supplementary Table 2 of the original publication (9). GWAS of ICV and hippocampal volumes were performed for each site separately, controlling for age, sex, and, when applicable age^2, population stratification variables, study site, and diagnosis (when applicable). Summary statistics, including effect estimates of the genetic variant with ICV or hippocampal volume under an additive model, were exchanged to perform a fixed-effects meta-analysis weighting for sample size in METAL (8). After the final meta-analysis, variants were excluded if they were only available for fewer than 5,000 individuals.

Removal of duplicated individuals

Subject overlap between all PGC ADHD and ENIGMA cohorts was evaluated using a checksum algorithm to ensure the robustness of our results, given that some analyses were sensitive to the presence of duplicate individuals. For each individual, ten checksum numbers were created based on ten batches of 50 SNP genotypes and compared between individuals from both consortia. Based on these comparisons no subjects needed to be removed from the data sets. As no Danish cohort was included in the ENIGMA or CHARGE study, we assumed that there is no sample overlap between cohorts studying brain volume and iPSYCH.

GWAS meta-analysis of ENIGMA and CHARGE data sets

To increase the sample size for the hippocampal volume and ICV data, summary statistics of GWAS-MA results from ENIGMA (4) (after removal of ADHD cases) and CHARGE (9, 10) were combined using a fixed-effects sample size-weighted meta-analysis framework as implemented in METAL (8). After the final meta-analysis, variants were excluded if they were only available for fewer than 5,000 individuals or a MAF ≤0.005. After filtering, the meta-analyses results included more than 9,145,464 markers. Importantly, the ENIGMA and CHARGE discovery data sets only included cohorts of European ancestry (all individuals had both imaging and genetics data). This overview is presented in the original publication of Adams and colleagues (9) in Supplementary Table 1.

Linkage disequilibrium score regression (LDSR)

For LDSR, each GWAS-MA data set underwent additional filtering. Only markers overlapping with HapMap Project Phase 3 SNPs and passing the INFO score ≥0.9 and MAF ≥0.01 filters were included (where available). SNPs with missing values, duplicate rs-numbers, too low a sample size (where available SNPs with an effective sample size less than 0.67 times the 90th percentile of sample size were removed), or that were strand-ambiguous - as well as indels - were removed. As described in the original ADHD GWAS-MA paper (1), for LDSR analysis the European only subset was used (n_{cases}=19,099 and $n_{controls}$=34,194), since LDSR requires linkage disequilibrium [LD] data from a sample of comparable ethnic background). For the ENIGMA amygdala results, the mean χ^2 was too low (1.0) to reliably estimate SNP heritability using LDSR. **Table 1** shows genetic correlations between the regional brain volumes; subcortical volumes are not strongly genetically correlated with ICV.

The analyses used a two-step procedure with the LD-scoring analysis package (11). An unconstrained regression estimated regression intercepts for each pair of phenotypes. Since we adopted protocols to exclude sample overlap, we also performed the analyses with regression intercept

for the genetic correlation analysis defined as zero (**Table S2**). To compute p-values, standard errors were estimated using a block jackknife procedure.

SNP effect concordance analysis (SECA)

Post-processing of genetic data

To statistically compare the ADHD and six brain volume GWAS-MAs, we used SNPs passing quality control and filtering rules (for ADHD GWAS-MA INFO ≥0.9 and MAF ≥0.01 and for ENIGMA and CHARGE GWAS-MA RSQ ≥0.5 and MAF ≥0.005) in all data sets. With these data, we performed a clumping procedure in PLINK (12) to identify an independent SNP from every LD block across the genome. The clumping procedure was performed separately for each of the brain volume GWAS-MAs using a 500 kb window, with SNPs in LD (r^2 >0.2) in the European reference samples from the 1KGP1v3 (6). The SNP with the lowest p-value within each LD block was selected as the index SNP representing that LD block and all other SNPs in the LD block were dropped from the analysis. The result after applying the clumping procedure was sets of independent SNPs representing the total variation explained across the genome conditioned on the significance in each brain volume GWAS-MA. For each of these sets of SNPs, we then determined the corresponding ADHD GWAS-MA test statistic for each independent, index SNP and used these data sets for the subsequent analyses.

Tests of pleiotropy and concordance

We used SNP Effect Concordance Analysis (SECA) (13) to determine the extent and directionality of genetic overlap between ADHD and each brain volume. Within SECA we performed a global test of pleiotropy using a binomial test at 12 p-value levels: P ≤(0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9). For a given brain volume and ADHD paired set, we separately ordered SNPs based on their p-value for association with each trait. For each of the 12 p-value levels, we determined the total number of

SNPs overlapping between the two traits at each p-value threshold and compared that number to the expected random overlap under the null hypothesis of no pleiotropy using a binomial test. In total, 144 comparisons were performed. We tallied the number of comparisons with evidence of overlap at a nominally significant level of P ≤0.05. To evaluate the global level of pleiotropy, we generated 1,000 permuted data sets for a given brain volume to ADHD comparison and determined, if the number of significance thresholds with genetic overlap was significantly greater than chance.

Similarly, we estimated concordance, the agreement in SNP effect directions across two traits. We determined whether or not there was a significant (P ≤0.05) positive or negative trend in the effect of the overlapping SNPs at each of the 12 p-value thresholds. This was done using a two-sided Fisher's exact test. The direction of effect for each SNP was determined by the sign of the SNP regression coefficient (OR or beta value) from each meta-analysis. In the ADHD GWAS-MA, an odds ratio >1 for a SNP indicates that the A1 reference allele was associated with an increased risk of developing ADHD (an odds ratio <1 indicates a protective allele). A positive Beta value for a SNP in a brain volume GWAS-MA indicates that the A1 reference allele of that SNP is associated with an increase in brain volume (a negative Beta value indicates that the A1 reference allele of that SNP is associated with a reduction in brain volume). We estimated the global level of concordance between a given brain trait and ADHD by generating 1 000 permuted data sets, repeating the Fisher's exact test procedure, and determined if the number of significant overlapping thresholds was significantly greater than chance (see Nyholt et al., 2014 (13) for details of the SECA analysis).

In total, we tested for pleiotropy and concordance between ADHD and six brain volumes. In accordance with the number of tests performed, we set a Bonferroni-corrected significance level at $P=0.05/(2*6)=4.17x10^{-3}$.

Independent genome-wide significant markers and loci

LD-independent markers associated at P <$1x10^{-5}$ were defined using the clump flag in PLINK v1.9 (3). Clumping was used to group additional associated markers within a 0.5 Mb window surrounding the index SNP. Markers were grouped to the index SNPs if they were also associated (P <0.001) and were in LD with the index SNP (r^2 >0.1). A genome-wide significant locus was defined as the physical region containing the identified LD independent index SNPs and their correlated variants (r^2 >0.8) with P <0.001. Associated loci within 250 kb of each other were merged. All LD statistics were calculated using the 1KGP3v5 (2) reference haplotypes.

SNP sign test in the intelligence GWAS-MA

We performed sign tests to investigate a potential accumulation of same or opposite direction effects of SNPs between ADHD+ICV, ADHD, and ICV GWAS-MA data and the intelligence GWAS-MA data(14). The ADHD+ICV GWAS-MA data were clumped to define independent loci (Supplementary Methods) for all variants with P<$1x10^{-5}$ and P<$1x10^{-4}$ in the ADHD+ICV GWAS-MA using 1KGP3v5 data on European ancestry populations as reference. Based on the negative genetic correlation between ADHD and intelligence, we expected an overrepresentation of discordant SNP effects. In contrast, the positive genetic correlation between ICV and intelligence guided us in specifically looking for concordant SNP effects. However, for the ADHD+ICV GWAS-MA data set we did not favor any directionality a priori and therefore tested for both same and opposite direction effects in the intelligence data set(14). The proportion of variants with a concordant or discordant direction of effect in the intelligence GWAS-MA was evaluated using a binomial test against a null hypothesis of 0.5 (i.e. chance level). This test was done for SNPs, which (1) passed the p-value threshold of P<$1x10^{-5}$ (64 LD-independent SNPs) and P<$1x10^{-4}$ (327 LD-independent SNPs) in the ADHD+ICV GWAS-MA and (2) showed smaller p-values in the

ADHD+ICV GWAS-MA compared to the ADHD and ICV GWAS-MA individually (43 and 225 LD-independent SNPs). We set a Bonferroni-corrected significance level at P=0.05/(2*3)=0.00833.

Weighted meta-analysis of ADHD and brain volume data sets

Independent of the results of the global overlap analyses, we also performed meta-analyses combining the results from the ADHD GWAS-MA with results from GWAS-MAs of brain volumes (amygdala, nucleus accumbens, caudate nucleus, hippocampus, putamen, and ICV). This was done using a modified sample size-based weighting method, integrating the binary ADHD trait (ADHD risk) with the continuous trait (brain volume traits), as described in Demontis et al.(1). For the meta-analyses, modified sample size-based weights were derived to account for the respective heritability, genetic correlation, and measurement scale of the GWASs. The adjusted samples sizes reflect differences in power between the studies due to measurement scale and relative heritability that is not captured by sample size. Thereby, the contribution of the continuous phenotype's GWAS to the meta-analysis is reduced based on imperfect correlation with the dichotomous phenotype of interest (in this case ADHD risk). The adjustments are computed based on the sample and population prevalence of the dichotomous phenotype, the estimated SNP heritability of the two phenotypes (liability scale for dichotomous phenotype), and the genetic correlation between the two phenotypes, as well as the average SNP LD score, and the number of SNPs. Heritability and genetic correlation values to compute these weights are computed using LD score regression (11) as described before. For a comprehensive description of the method for meta-analysis of continuous and dichotomous phenotype and notes on the implementation please see the supplementary information of the original ADHD GWAS-MA publication (1). For all brain volumes, we also performed naive meta-analyses given the low genetic correlations with ADHD risk observed. Correcting for meta-analyzing six brain phenotypes with ADHD, we set the threshold for genome-wide significance at $P=5x10^{-8}/6=8.33x10^{-9}$. Additionally, loci were considered cross-disorder

relevant if (i) those loci were genome-wide significant in the cross-phenotype meta-analysis, (ii) and/or had a cross-phenotype p-value, which was improved by at least one order of magnitude, and (iii) had a cross-phenotype z-score, which (at least) equaled the ones observed in the GWAS-MAs for the individual phenotypes. The LD score intercept and ratio of the individual and meta-analyzed summary statistics are presented in **Table** S**23** in order to compare the estimates of the overall genetic signal.

The percentage variance explained by each genome-wide significant index SNP was determined based on the ENIGMA2 data set after correction for covariates using the following equation:

$$\frac{R^2_{g|c}}{1 - R^2_c} = (t^2/((n-k-1)+t^2)) * 100$$

where the *t*-statistic is calculated as the beta coefficient for a given SNP from the regression model (controlling for covariates) divided by the standard error of the beta estimate, and where *n* is the total number of subjects and *k* is the total number of covariates included in the model (*k*=10). $R^2_{g|c}$ is the variance explained by the variant controlling for covariates, and R^2_c is the variance explained by the covariates alone. $R^2_{g|c}/(1 - R^2_c)$ gives the variance explained by the genetic variant after accounting for covariate effects.

Gene-based and gene-set analyses for ADHD+brain GWAS-MA data

Genome-wide summary statistics of (i) ADHD GWAS-MA, (ii) individual brain GWAS-MAs, and (iii) weighted meta-analysis data for combined ADHD and brain volume GWAS-MAs were used as input for gene-based analyses. For the ADHD+brain GWAS-MA, only SNPs shared between ADHD and brain volume data sets were included. Statistical analyses were performed using the Multi-marker Analysis of GenoMic Annotation (MAGMA) software package (version 1.05, (15)). Genome-wide SNP data from a reference panel 1KGP1v3 (6) was annotated to NCBI Build 37.3 gene locations using a symmetric 100 kb flanking window. Both files were downloaded from http://ctglab.nl/software/magma. The gene annotation file was used to map genome-wide SNP data from the different studies (ADHD GWAS-MA,

brain GWAS-MAs, and ADHD+brain GWAS-MA), to assign SNPs to genes followed by the calculation of gene-based p-values. This step was done for each of the data sets individually. For the gene-based analyses, single SNP p-values within a gene were transformed into a gene-statistic by taking the mean of the χ^2-statistic among the SNPs in each gene. To account for LD, the 1KGP1v3 (6) was used as a reference to estimate the LD between SNPs within (the vicinity of) the genes (http://ctglab.nl/software/MAGMA/ref_data/g1000_ceu.zip). Gene-wide p-values were converted to z-values reflecting the strength of the association of each gene with the phenotype, with higher z-values corresponding to stronger associations. Genome-wide gene-based results were considered significant if they reached the Bonferroni-corrected P-value-threshold for testing 18,310 genes ($P<2.731x10^{-6}$; for gene-based results of all genes see **Tables S4–S9**). Then, we assessed the number of significant genes overlapping between the ADHD GWAS-MA results and the cross-trait ADHD+brain GWAS-MA results. Of those overlapping genes, we considered those as cross-trait relevant if (i) those genes were genome-wide significant in the cross-trait MA, (ii) and had a cross-trait association p-value that was smaller compared to the separate analyses of ADHD and brain volume, and (iii) had a nominally significant ($P<0.05$) P-value in the individual gene-based brain trait result. The latter criterion was established in order to distinguish the 'true' cross-trait effect from increase in association signal that is purely related to an increase in samples size when combining the two GWAS-MA data sets. Genes, meeting these criteria, were reported and selected for further investigation.

Based on our finding that *SEMA6D* is a key locus contributing to both ADHD risk and ICV – a loci involved in neuronal migration and axonal path finding – we investigated, whether neurite outgrowth-related genes in general have a role in ADHD–ICV genetic overlap. For the gene-set analyses we chose to use a pre-defined gene-set of 45 neurite outgrowth genes . In the initial study, Poelmans and colleagues investigated the presence of genomic convergence in the top findings of the five published GWASs of ADHD. Then, they carried out bioinformatics pathway analyses, using the Ingenuity and BiNGO tools, as

well as a systematic literature analysis of 85 genes from the five published GWASs containing SNPs associated with ADHD at a p value <0.0001. Out of those 85 top-ranked ADHD candidate genes, 45 genes encode proteins that fit into a neurodevelopmental network involved in directed neurite outgrowth. Moreover, the authors added data on CNVs in patients with ADHD and data from animal studies and this provided further support for the involvement of this network in ADHD etiology. Additionally, they could show that several network proteins are directly modulated by stimulants (commonly used treatment for ADHD).

Subsequent to the genome-wide gene-based analysis, we also tested, whether genes in the neurite-outgrowth gene-set (defined previously, N_{genes}=45 (16)) were jointly associated with results of the weighted meta-analytic data of ADHD+ICV using self-contained and competitive testing (17). For the gene-set analyses, we used an intercept-only linear regression model including a subvector corresponding to the genes in the gene-set. This self-contained analysis tests whether the gene-set shows any association with the phenotype at all by evaluating whether the regression coefficient of this regression is larger than 0. Next, we tested whether genes in the gene-set were more strongly associated with phenotype than all other genes in the genome. Therefore, the regression model was then expanded including all genes outside the gene-set. With this competitive test, the differences between the association of the neurite-outgrowth gene-set to genes outside this gene-set is tested, accounting for the polygenic nature of such a complex trait. To account for the potentially confounding factors of gene size and gene density, both variables as well as their logarithms were included as covariates in the competitive gene-set analysis. Since self-contained tests do not take into account the overall level of association across the genome, gene size (number of principal components, or SNPs), and gene density, we were particularly interested in the competitive test for the current analysis. Basically, a significance in the self-contained tests but not the competitive test, suggests that the effect of the gene-set is not different from the background effect that captures the polygenic nature of ADHD.

Moreover, a non-significant competitive p-value can be interpreted as not being able to disentangle the part of the polygenicity attributable to the genes in the gene set versus the polygenicity "remaining" (i.e. not captured by the set) on the rest of the genome and not that the selected gene-set has no effect on the outcome. Subsequently, we tested whether the gene-set was associated with the two individual data sets as well. In this, the same procedure was followed for analysis of the ADHD GWAS-MA and ENIGMA+CHARGE ICV GWAS-MA summary statistics individually. *Post-hoc*, the individual genes in the set were investigated, by reviewing gene test-statistics of the weighted ADHD+ICV GWAS-MA results. Genes of the neurite-outgrowth set were considered gene-wide significant, if they reached the adjusted Bonferroni correction threshold (P=0.05/45=0.00111). Subsequently, we reviewed gene-based associations in the ADHD GWAS-MA and ENIGMA+CHARGE ICV GWAS-MA results separately. For genome-wide gene-based comparisons we considered results significant, if they reached the Bonferroni-corrected P-value-threshold for testing 18,411 genes ($P<2.716x10^{-6}$). Then, we assessed the number of significant genes overlapping between the ADHD GWAS-MA results and the cross-trait ADHD+brain GWAS-MA results. Of those overlapping genes, we considered those as cross-trait relevant if (i) those genes were genome-wide significant in the cross-trait MA, (ii) and had a cross-trait association p-value that was smaller compared to the separate analyses of ADHD and brain volume, and (iii) had a nominally significant (P<0.05) P-value in the individual gene-based brain trait result. The latter criterion was established in order to distinguish the 'true' cross-trait effects from increase in association signal that is purely related to an increase in samples size when combining the two GWAS-MA data sets. Genes, meeting these criteria, were reported and selected for further investigation.

Significant genes with lower association p-values in the meta-analysis, compared to the separate analyses of ADHD and ICV, were reported in **Table S10**.

Expression quantitative trait loci and brain gene expression

To assess potential functionality in (brain) tissues, we tested the identified risk variants (**Table 4**) for association with gene expression. Expression quantitative trait loci (eQTL) were examined using data from the GTEx portal (https://www.gtexportal.org/home/) (18). The data is presented in Table S7 and is shown as normalized effect sizes (NES) and p-values. NES describes the slope of the linear regression of normalized expression data versus the three genotype categories using single-tissue eQTL analysis, representing eQTL effect size. The normalized expression values are based on quantile normalization within each tissue, followed by inverse quantile normalization for each gene across samples. The p-value results from a t-test that compares observed beta from single-tissue eQTL analysis to a null beta of 0. In addition, blood eQTL data were queried using the Blood eQTL Browser (http://genenetwork.nl/bloodeqtlbrowser/) (19).

We also investigated the spatio-temporal expression pattern in brain tissue for genes with significantly associated variants in the approaches described earlier (**Table 4**) using data from the Human Brain Transcriptome Project (http://hbatlas.org). We assessed messenger RNA (mRNA) expression trajectories in six regions of the developing and adult human brain. Spanning periods from embryonic development to late adulthood, this data set provides genome-wide exon-level transcriptome data generated using the Affymetrix GeneChip Human Exon 1.0 SS Arrays from over 1,340 tissue samples sampled from both hemispheres of *postmortem* human brains (n=57) (20). Gene expression over the lifespan from the spatio-temporal atlas was graphed using custom R scripts (20).

URLs

http://enigma.ini.usc.edu/download-enigma-gwas-results/

https://www.med.unc.edu/pgc/results-and-downloads

https://github.com/bulik/ldsc

https://neurogenetics.qimrberghofer.edu.au/SECA/

https://analysistools.nci.nih.gov/LDlink/

https://www.gtexportal.org/home/

http://hbatlas.org

http://ctglab.nl/software/MAGMA/ref_data/g1000_ceu.zip

http://locuszoom.sph.umich.edu/

DATA AVAILABILITY

The genome-wide summary statistics that support the findings of this study are available at the consortia websites.

PGC ADHD working group and the ADHD iPSYCH-SSI-Broad collaboration: https://www.med.unc.edu/pgc/results-and-downloads

ENIGMA and ENIGMA+CHARGE for ICV and hippocampus: http://enigma.ini.usc.edu/download-enigma-gwas-results/

SUPPLEMENTARY FIGURES

FIGURE S1 (a-h): Global evidence of pleiotropy between the ADHD GWAS and each brain volume GWAS (nucleus accumbens, amygdala, caudate nucleus, hippocampus, putamen, and intracranial volume). Plots show the results from SECA separated into separate panels, one for each comparison.

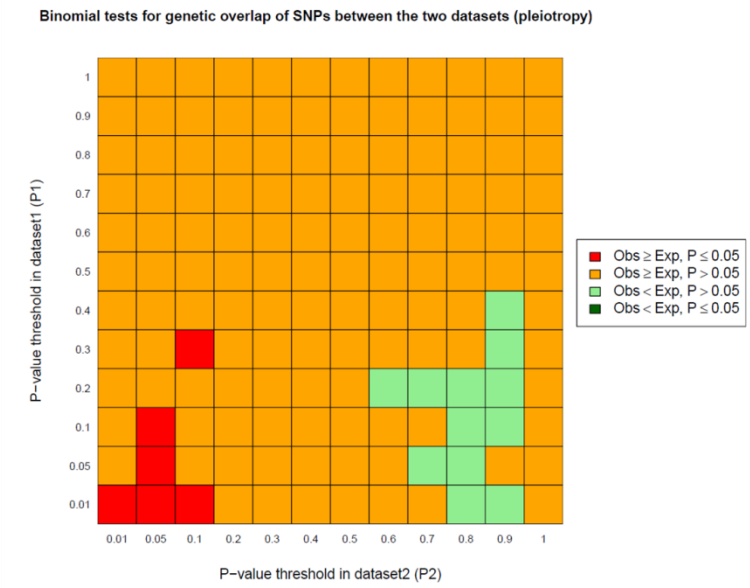

FIGURE S1 (a): Global evidence of pleiotropy between ADHD GWAS and nucleus accumbens volume. P1 in the plot is the ADHD GWAS and P2 is the nucleus accumbens GWAS. The global evidence for pleiotropy was not significant after accounting for multiple testing (P=0.034).

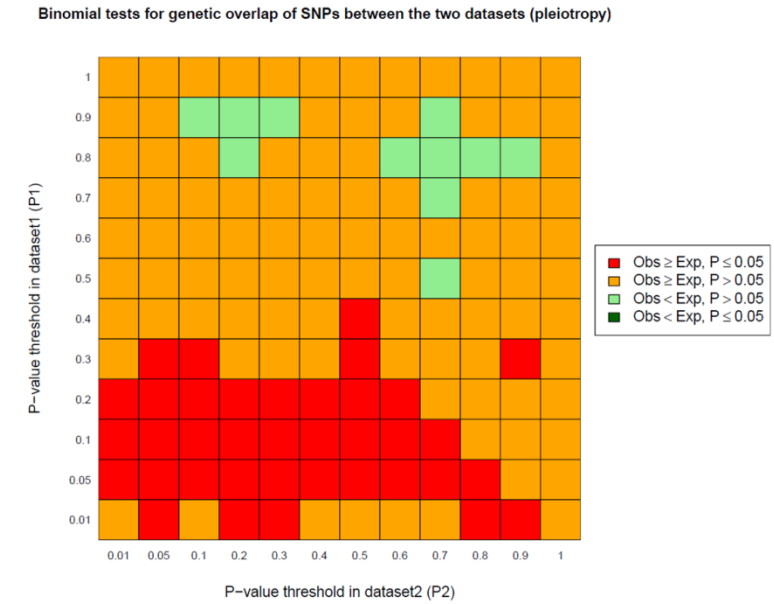

FIGURE S1 (b): Global evidence of pleiotropy between ADHD GWAS and amygdala volume. P1 in the plot is the ADHD GWAS and P2 is the amygdala GWAS. The global evidence for pleiotropy was significant after accounting for multiple testing (P<0.001).

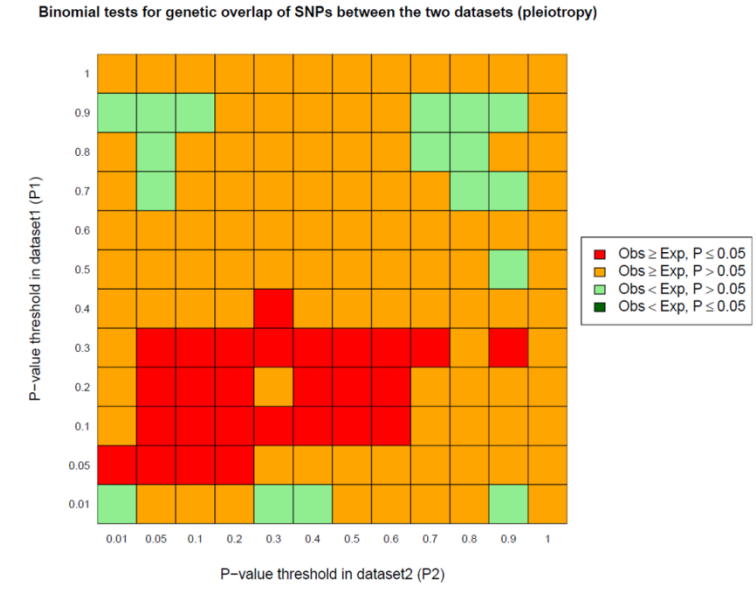

FIGURE S1 (c): Global evidence of pleiotropy between ADHD GWAS and caudate nucleus volume. P1 in the plot is the ADHD GWAS and P2 is the caudate nucleus GWAS. The global evidence for pleiotropy was significant after accounting for multiple testing (P<0.001).

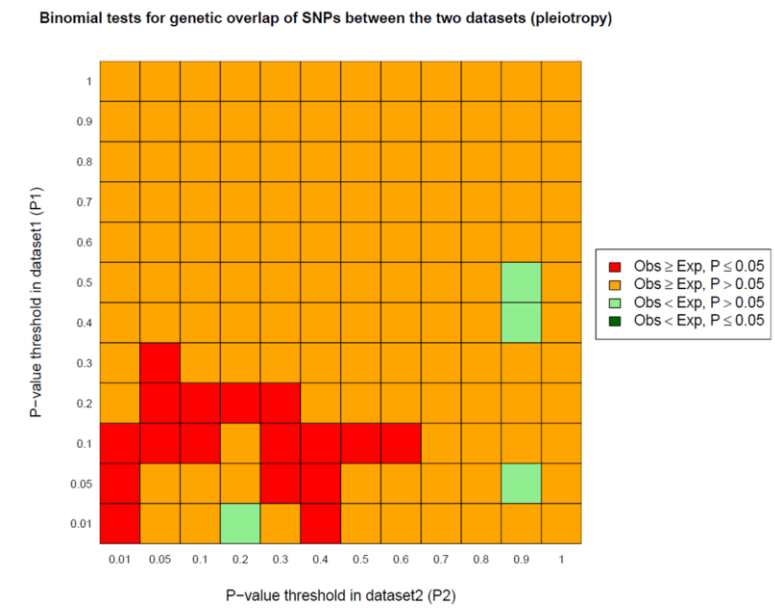

FIGURE S1 (d): Global evidence of pleiotropy between ADHD GWAS and hippocampus volume (ENIGMA+CHARGE GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the hippocampus GWAS. The global evidence for pleiotropy was significant after accounting for multiple testing (P=0.002).

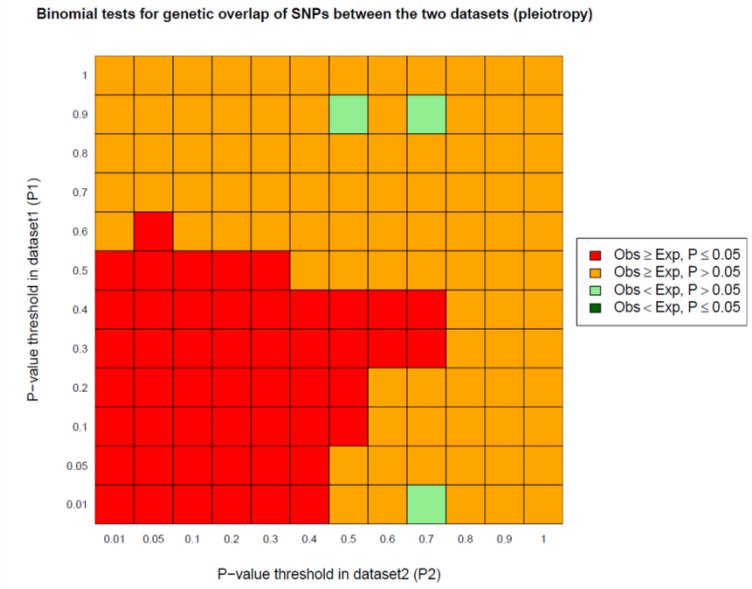

FIGURE S1 (e): Global evidence of pleiotropy between ADHD GWAS and intracranial volume (ENIGMA+CHARGE GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the intracranial volume GWAS. The global evidence for pleiotropy was significant after accounting for multiple testing (P<0.001).

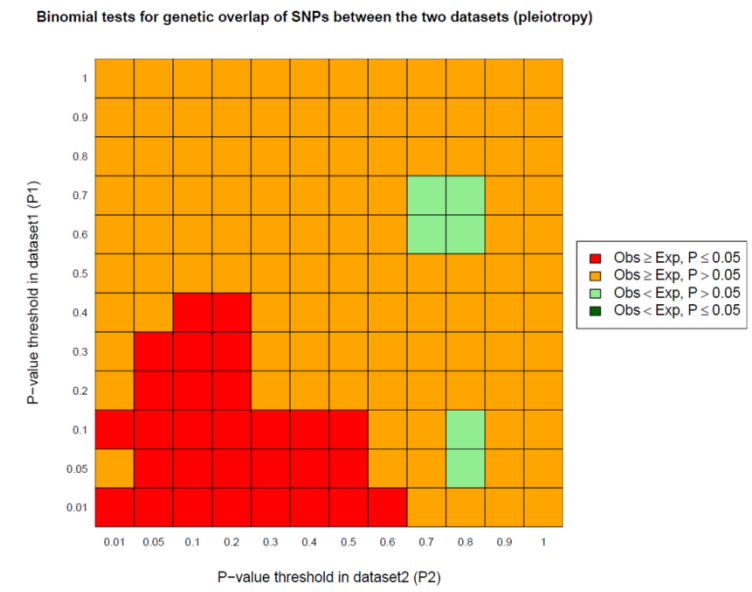

FIGURE S1 (f): Global evidence of pleiotropy between ADHD GWAS and putamen volume. P1 in the plot is the ADHD GWAS and P2 is the putamen volume GWAS. The global evidence for pleiotropy was significant after accounting for multiple testing (P<0.001).

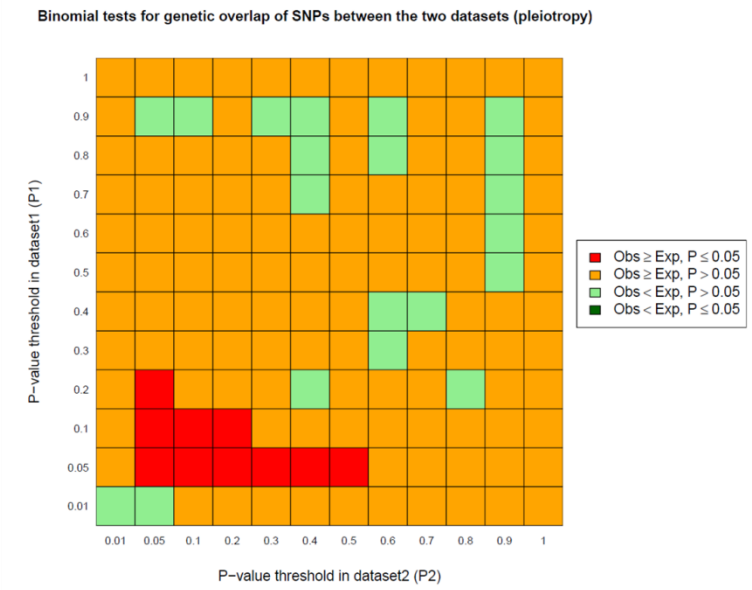

FIGURE S1 (g): Global evidence of pleiotropy between ADHD GWAS and hippocampus volume (ENIGMA only GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the hippocampus GWAS. The global evidence for pleiotropy was not significant after accounting for multiple testing (P=0.005).

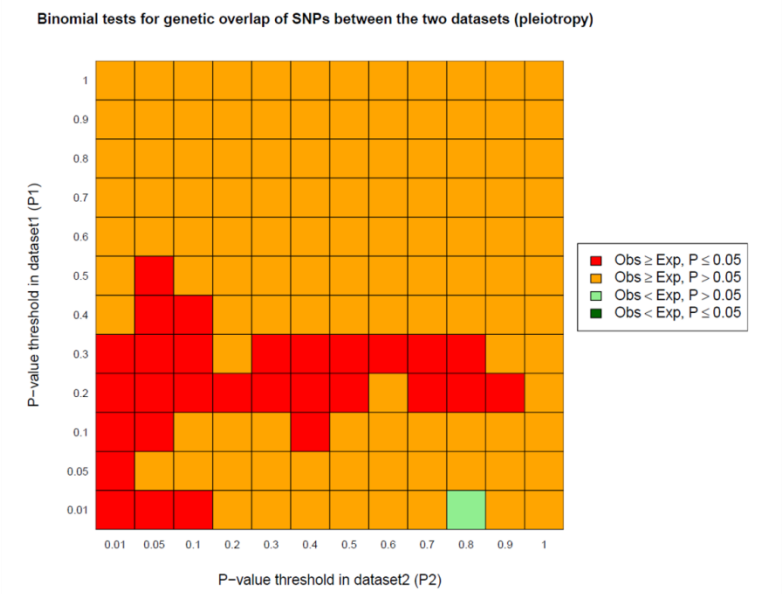

FIGURE S1 (h): Global evidence of pleiotropy between ADHD GWAS and intracranial volume (ENIGMA only GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the intracranial volume GWAS. The global evidence for pleiotropy was significant after accounting for multiple testing (P<0.001).

FIGURE S2 (a-h): Global evidence of concordance between the ADHD GWAS and each brain volume GWAS (nucleus accumbens, amygdala, caudate nucleus, hippocampus, putamen, and intracranial volume). Plots show the results from SECA separated into separate panels, one for each comparison.

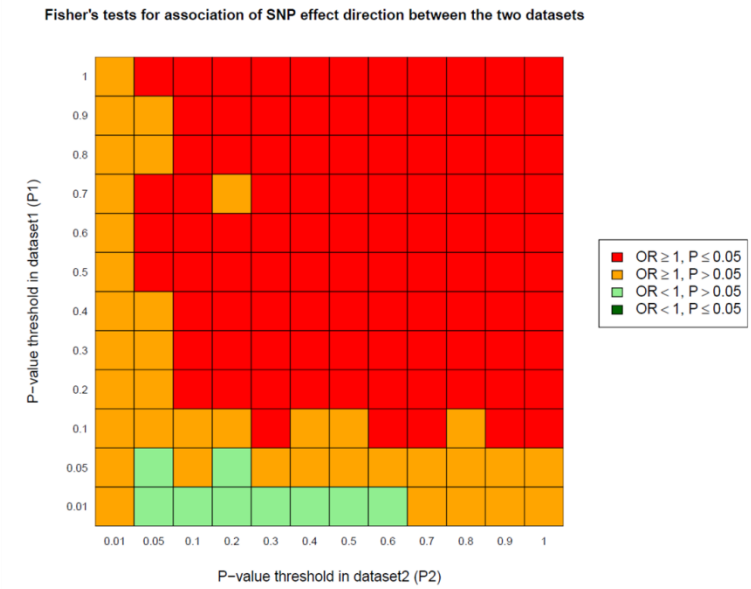

FIGURE S2 (a): Global evidence for concordant effects between ADHD GWAS and nucleus accumbens. P1 in the plot is the ADHD GWAS and P2 is the nucleus accumbens GWAS. The global evidence for positive concordance was significant after accounting for multiple testing (P=0.002).

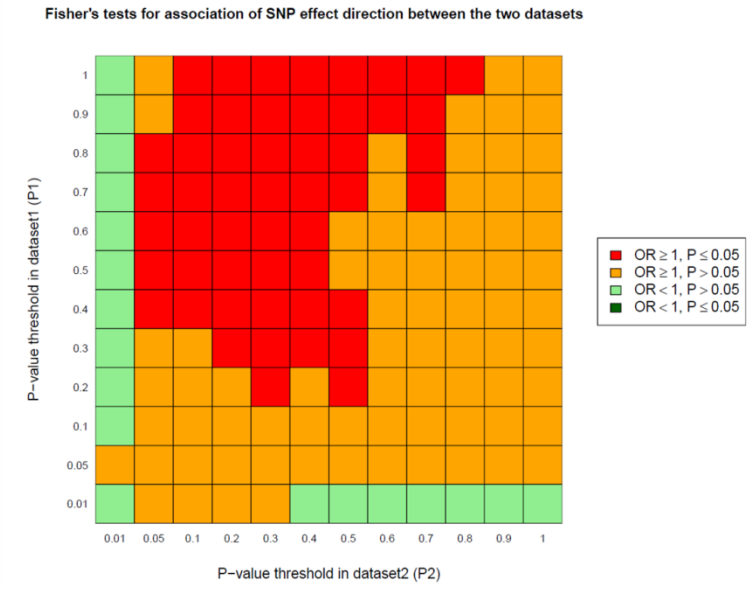

FIGURE S2 (b): Global evidence for concordant effects between ADHD GWAS and amygdala. P1 in the plot is the ADHD GWAS and P2 is the amygdala GWAS. The global evidence for concordance was not significant after accounting for multiple testing (P=0.006).

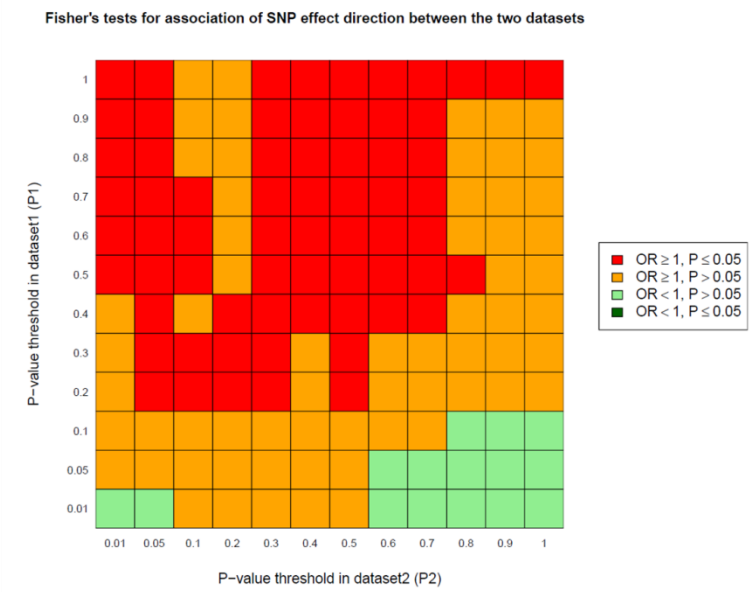

FIGURE S2 (c): Global evidence for concordant effects between ADHD GWAS and caudate nucleus. P1 in the plot is the ADHD GWAS and P2 is the caudate nucleus GWAS. The global evidence for positive concordance was significant after accounting for multiple testing (P=0.004).

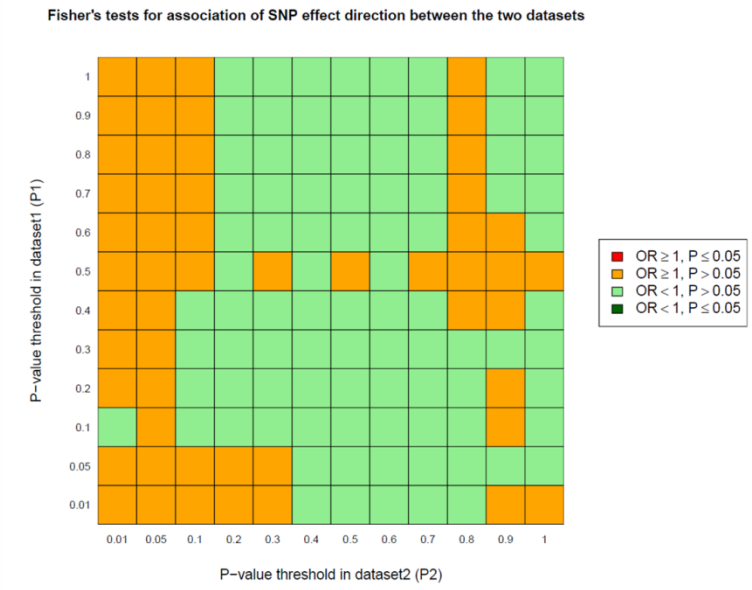

FIGURE S2 (d): Global evidence for concordant effects between ADHD GWAS and hippocampus volume (ENIGMA+CHARGE GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the hippocampus volume GWAS. The global evidence for concordance was not significant after accounting for multiple testing (P=1).

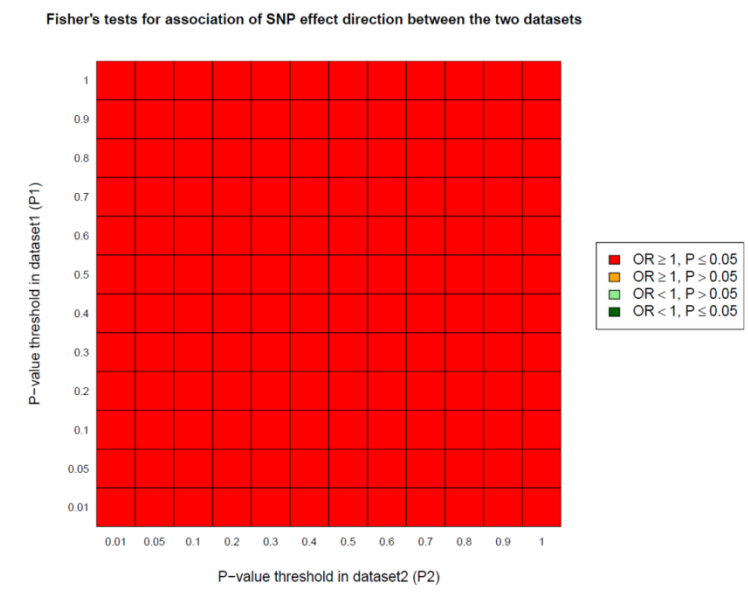

FIGURE S2 (e): Global evidence for concordant effects between ADHD GWAS and intracranial volume (ENIGMA+CHARGE GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the intracranial volume GWAS. The global evidence for negative concordance was significant after accounting for multiple testing (P<0.001).

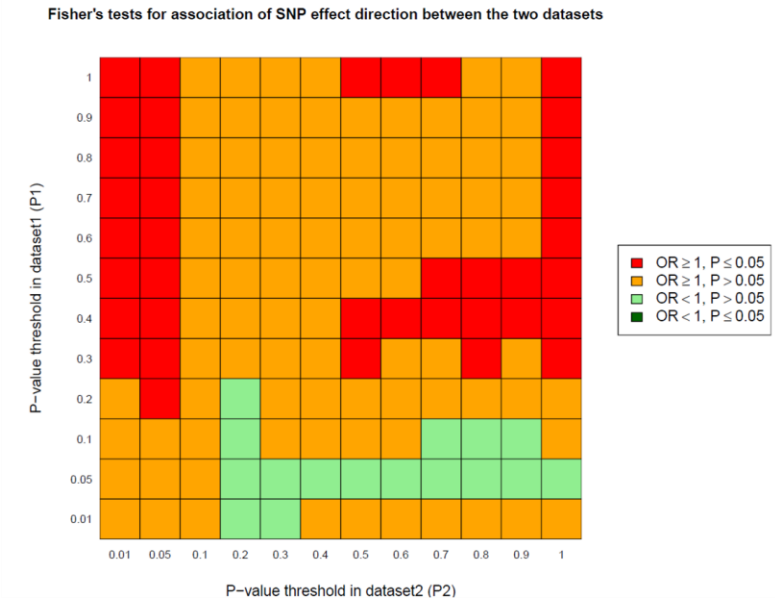

FIGURE S2 (f): Global evidence for concordant effects between ADHD GWAS and putamen. P1 in the plot is the ADHD GWAS and P2 is the putamen GWAS. The global evidence for concordance was not significant after accounting for multiple testing (P<0.001).

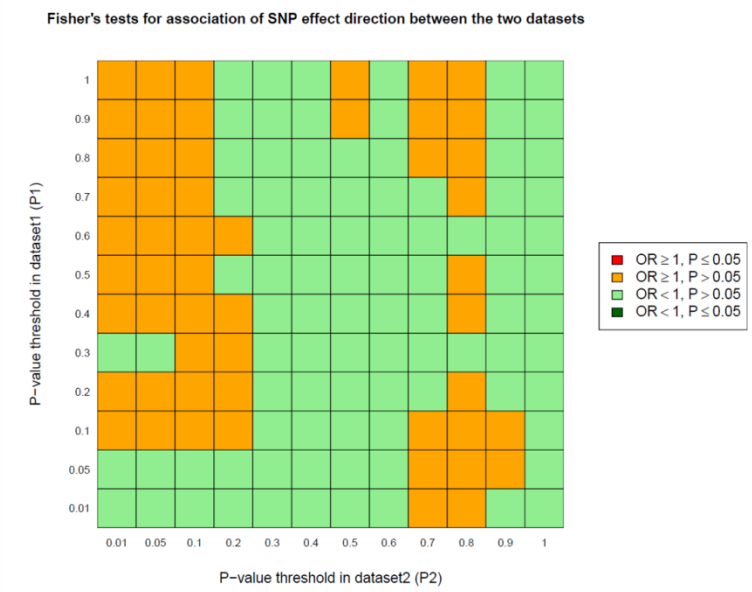

FIGURE S2 (g): Global evidence for concordant effects between ADHD GWAS and hippocampus volume (ENIGMA only GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the hippocampus volume GWAS. The global evidence for concordance was not significant after accounting for multiple testing (P=1).

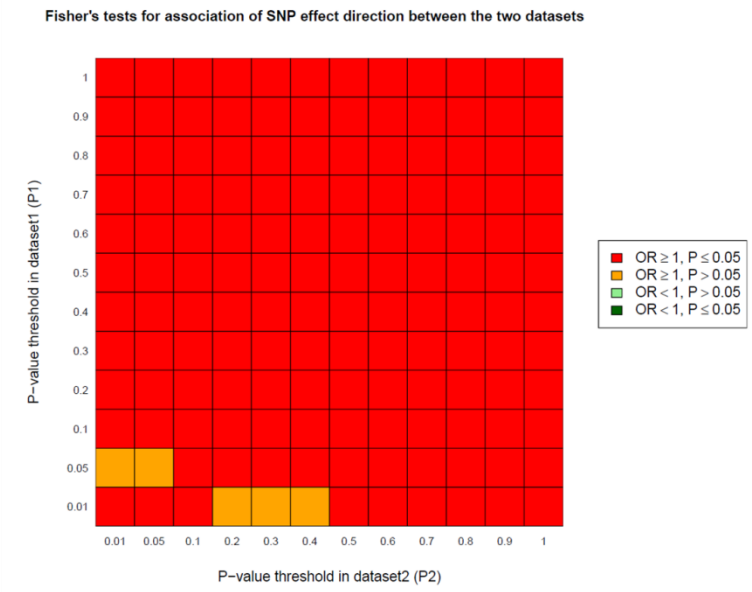

FIGURE S2 (h): Global evidence for concordant effects between ADHD GWAS and intracranial volume (ENIGMA only GWAS-MA). P1 in the plot is the ADHD GWAS and P2 is the intracranial volume GWAS. The global evidence for negative concordance was significant after accounting for multiple testing (P<0.001).

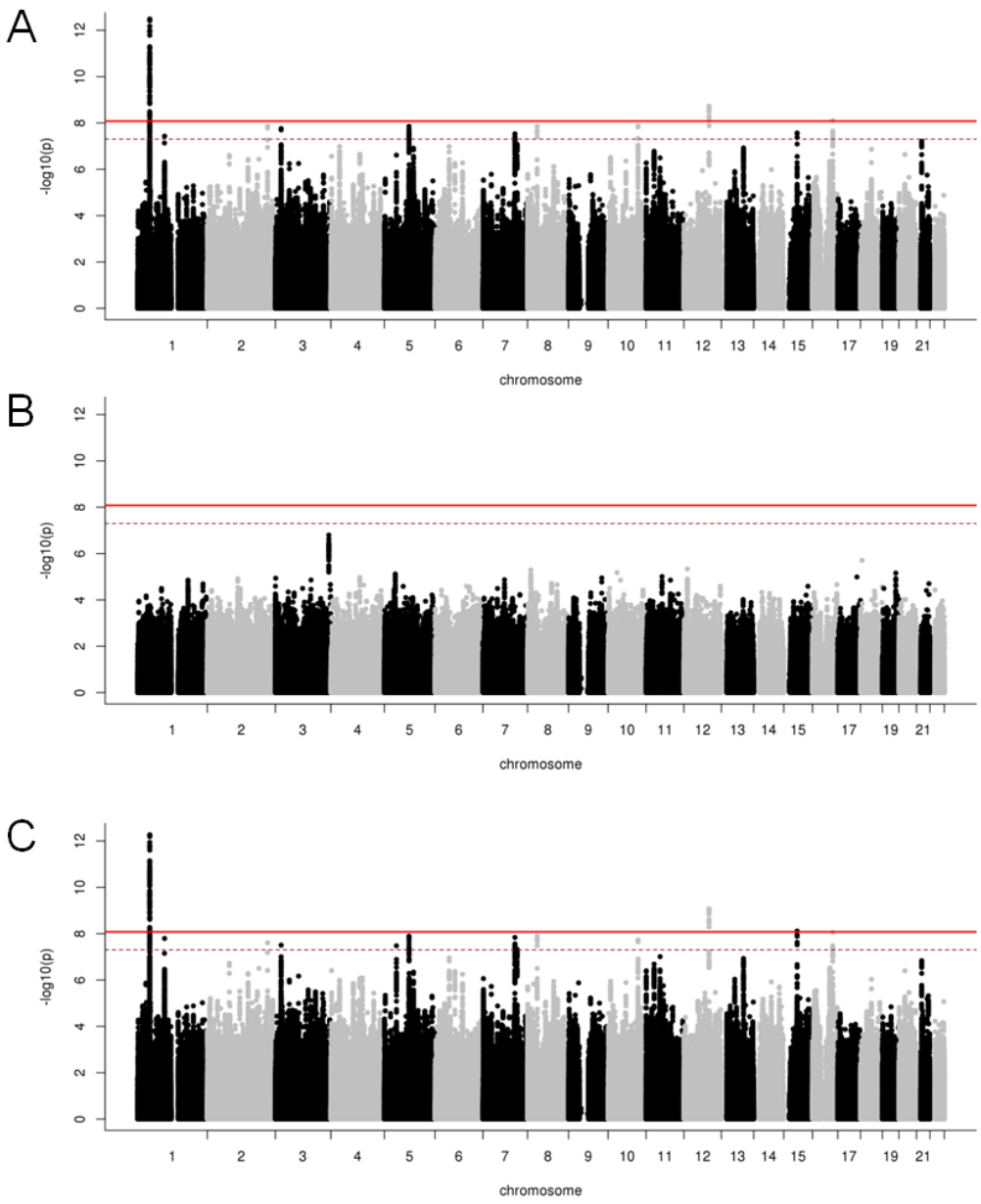

FIGURE S3. Common genetic variants associated with ADHD, nucleus accumbens and the meta-analysis of ADHD and nucleus accumbens. Manhattan plots in which every point represents a single genetic variant plotted according to its genomics position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the study-wide genome-wide significance of $P<8.33\times10^{-9}$ and the dashed dark red line represents the genome-wide significance of $P<5\times10^{-8}$. (A) PGC+iPSYCH ADHD GWAS-MA. (B) ENIGMA nucleus accumbens GWAS-MA. (C) ADHD+ nucleus accumbens weighted GWAS-MA.

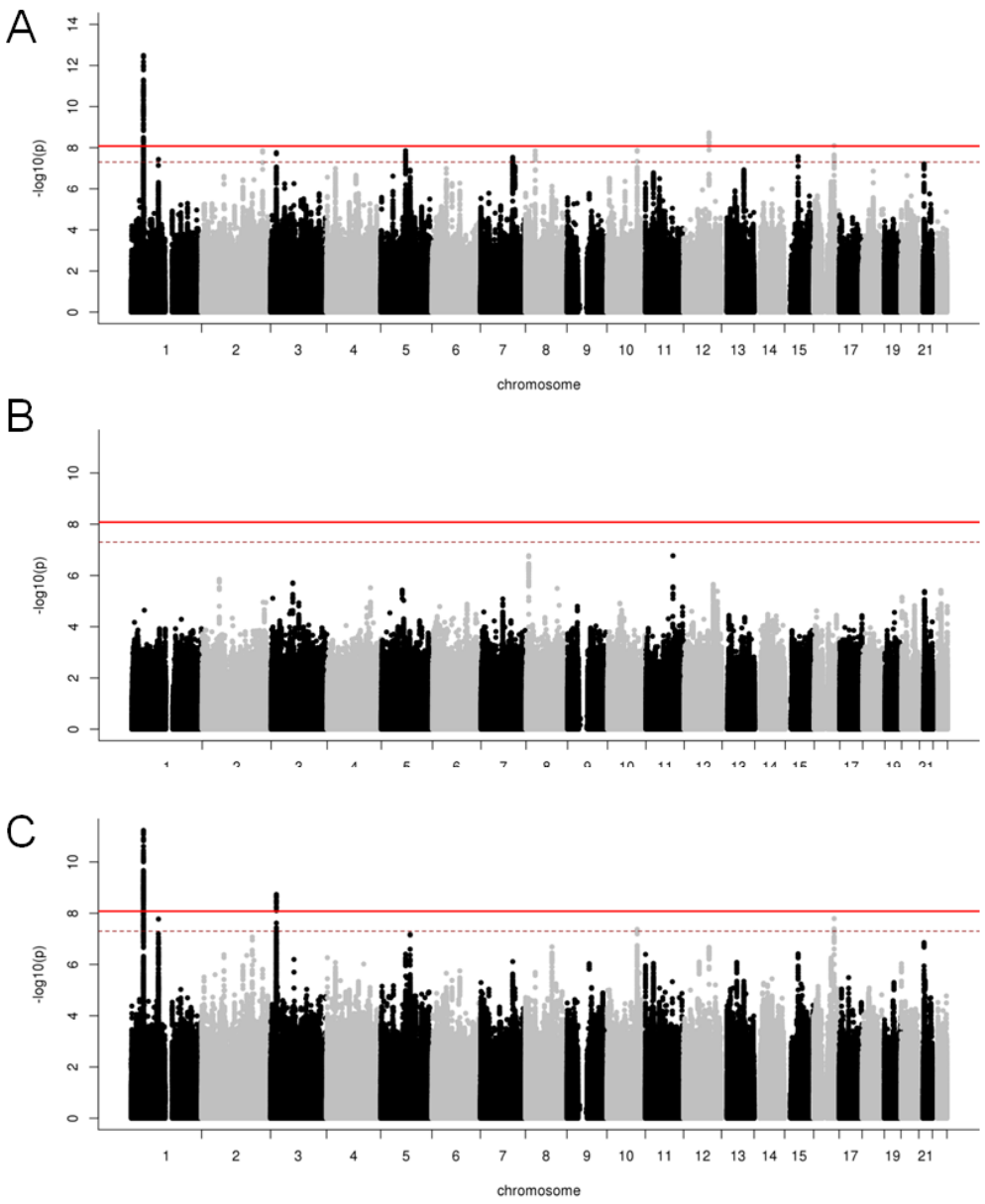

FIGURE S4. Common genetic variants associated with ADHD, amygdala and the meta-analysis of ADHD and amygdala. Manhattan plots in which every point represents a single genetic variant plotted according to its genomics position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the study-wide genome-wide significance of $P<8.33\times10^{-9}$ and the dashed dark red line represents the genome-wide significance of $P<5\times10^{-8}$. (A) PGC+iPSYCH ADHD GWAS-MA. (B) ENIGMA amygdala GWAS-MA. (C) ADHD+amygdala naive GWAS-MA.

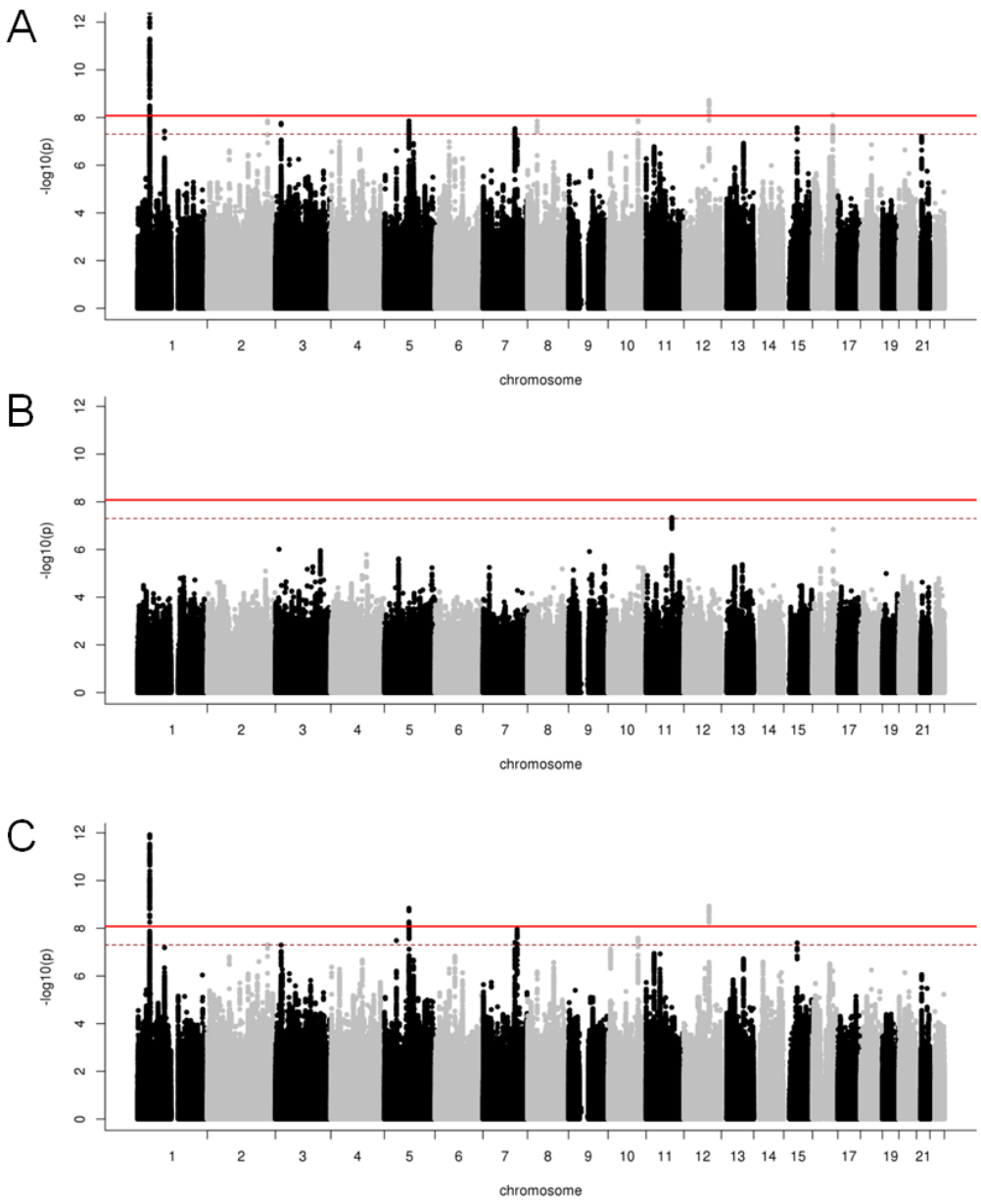

FIGURE S5. Common genetic variants associated with ADHD, caudate nucleus and the meta-analysis of ADHD and caudate nucleus. Manhattan plots in which every point represents a single genetic variant plotted according to its genomics position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the study-wide genome-wide significance of $P<8.33\times10^{-9}$ and the dashed dark red line represents the genome-wide significance of $P<5\times10^{-8}$. (A) PGC+iPSYCH ADHD GWAS-MA. (B) ENIGMA caudate nucleus GWAS-MA. (C) ADHD+caudate nucleus weighted GWAS-MA.

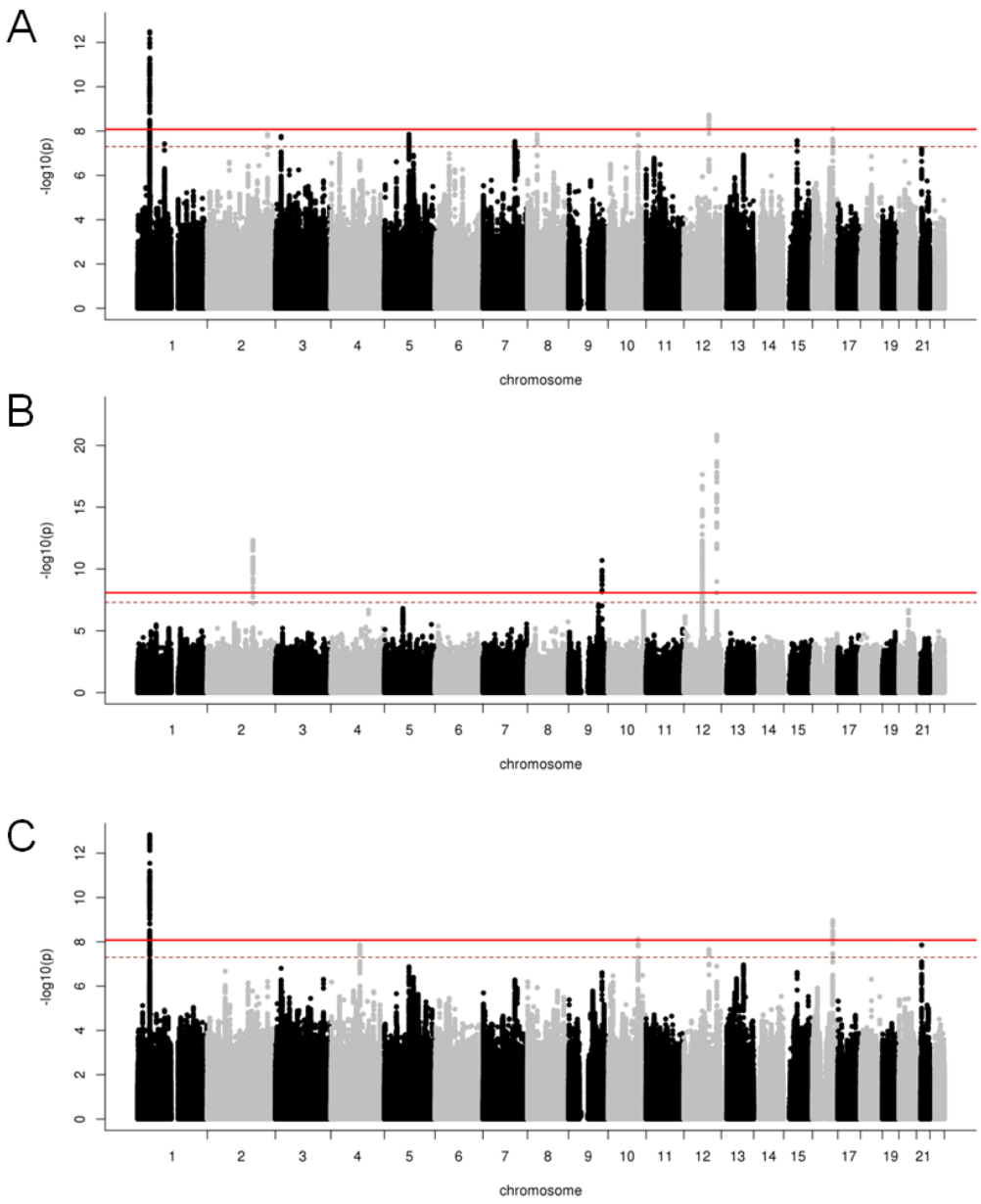

FIGURE S6. Common genetic variants associated with ADHD, hippocampus and the meta-analysis of ADHD and hippocampus. Manhattan plots in which every point represents a single genetic variant plotted according to its genomics position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the study-wide genome-wide significance of $P<8.33\times10^{-9}$ and the dashed dark red line represents the genome-wide significance of $P<5\times10^{-8}$. (A) PGC+iPSYCH ADHD GWAS-MA. (B) ENIGMA+CHARGE hippocampus GWAS-MA. (C) ADHD+hippocampus weighted GWAS-MA.

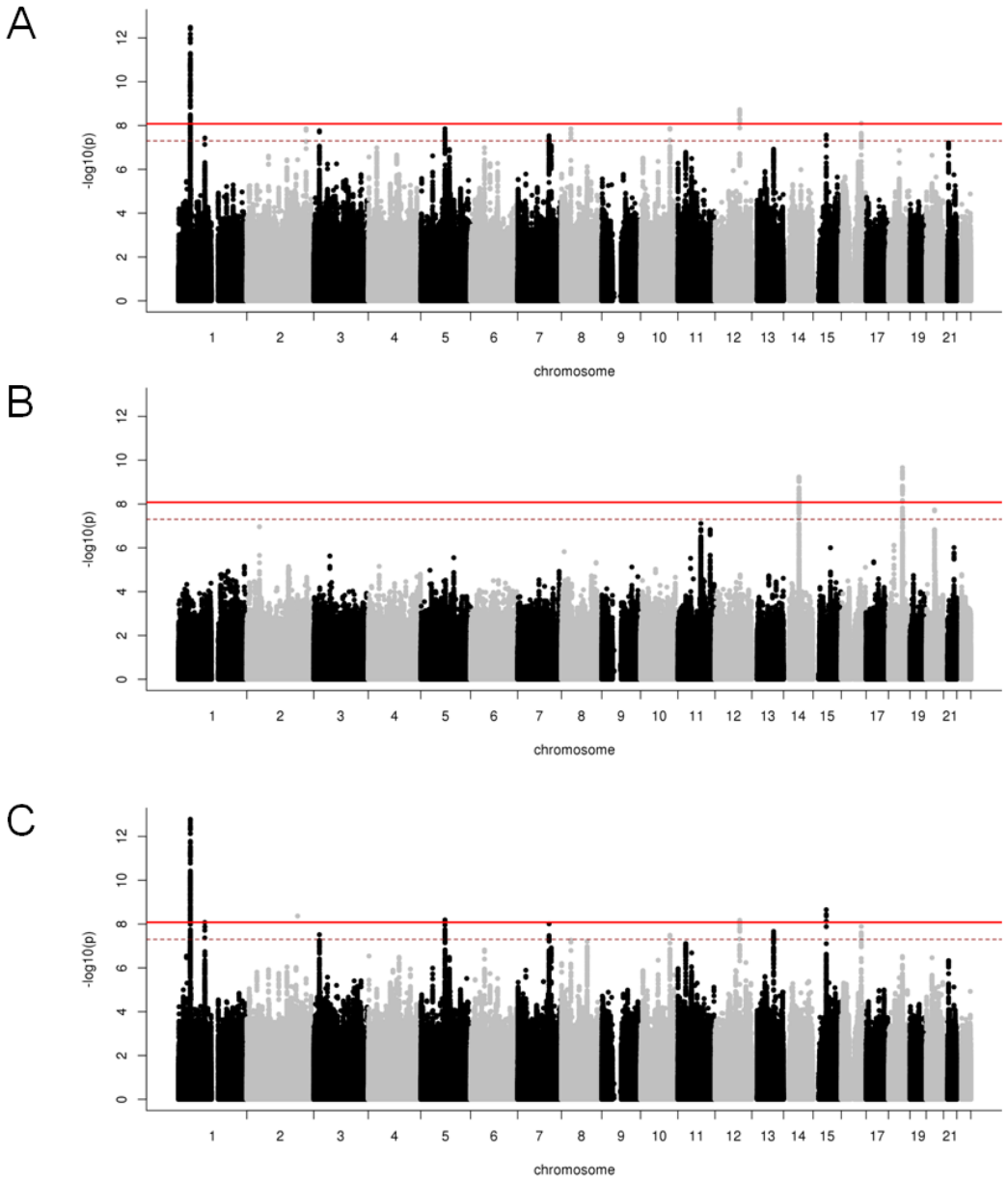

FIGURE S7. Common genetic variants associated with ADHD, putamen and the meta-analysis of ADHD and putamen. Manhattan plots in which every point represents a single genetic variant plotted according to its genomics position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the study-wide genome-wide significance of $P<8.33\times10^{-9}$ and the dashed dark red line represents the genome-wide significance of $P<5\times10^{-8}$. (A) PGC+iPSYCH ADHD GWAS-MA. (B) ENIGMA putamen GWAS-MA. (C) ADHD+putamen weighted GWAS-MA.

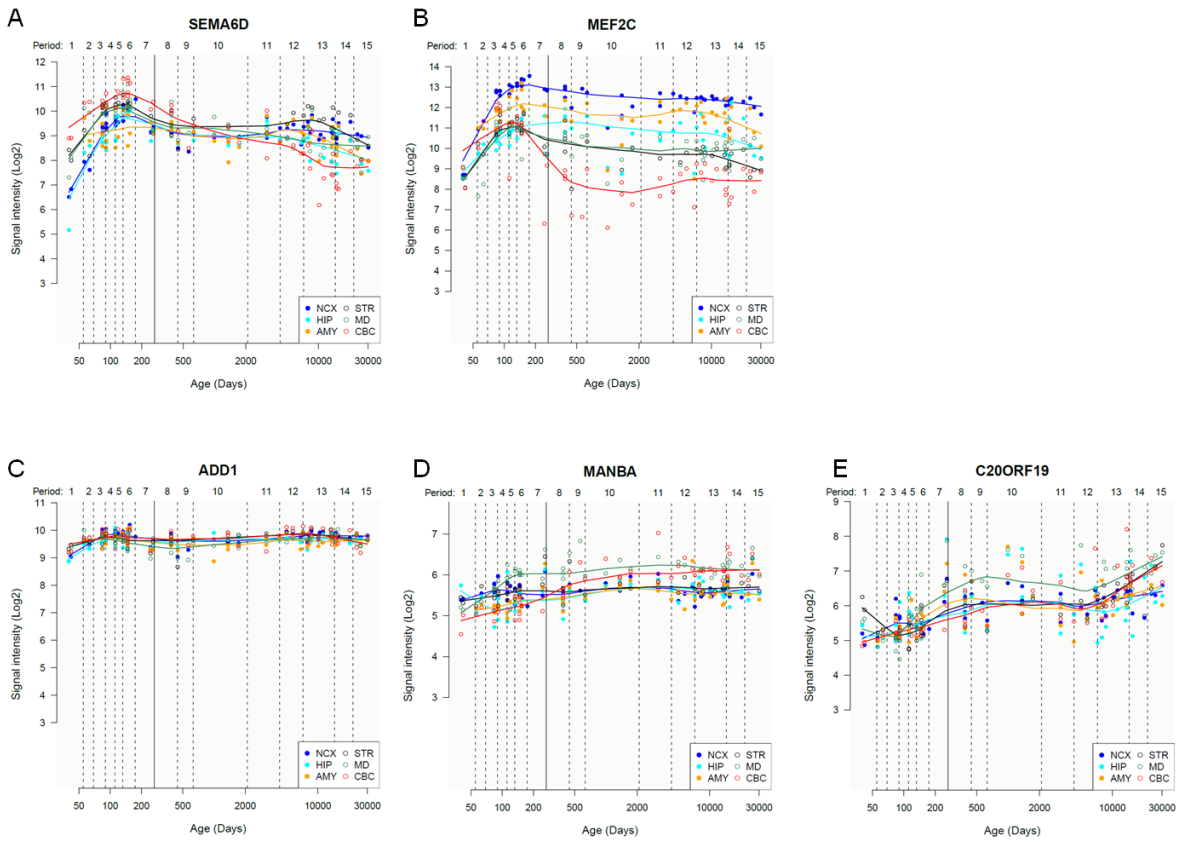

FIGURE S8. Expression trajectories of SEMA6D (A), MEF2C (B), ADD1 (C), MANBA (D), and C20ORF19 (alias KIZ (E)) in the developing and adult human brain. Line plots show the log_2-transformed gene exon array signal intensity from the early fetal period to late adulthood in six brain regions. The solid line between periods 7 and 8 (approximately post-conception day 280) separates prenatal from postnatal periods. Data were generated using Affymetrix GeneChip Human Exon 1.0 ST Arrays by the Human Brain Transcriptome project, and accessed via their publicly available database at http://hbatlas.org (20). The *FEZF1* gene was not present in the Human Brain Transcriptome database. Abbreviations: NCX=neocortex; HIP=hippocampus; AMY=amygdala; STR=striatum; MD=mediodorsal nucleus of the thalamus; CBC=cerebellar cortex.

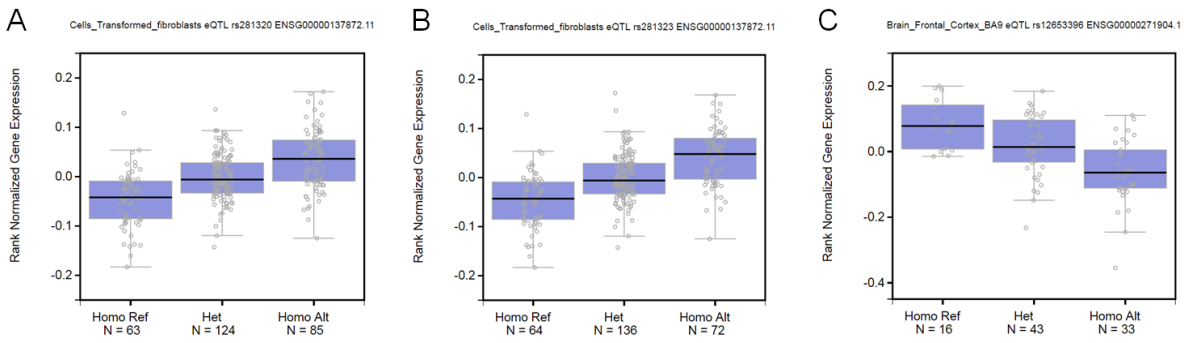

FIGURE S9. Effect of index SNPs from ADHD+brain meta-analyses on human gene expression. (A) Expression quantitative trait loci (eQTL) analysis in transformed fibroblasts demonstrates the effect of rs281320 on *SEMA6D* gene expression. (B) eQTL analysis in transformed fibroblasts demonstrates the effect of rs281323 on *SEMA6D* gene expression. (C) eQTL analysis in frontal cortex tissue demonstrates the effect of rs12653396 on *CTC-498M16.4* gene expression. The data used here is publicly from GTEx Analysis Release V6p (18).

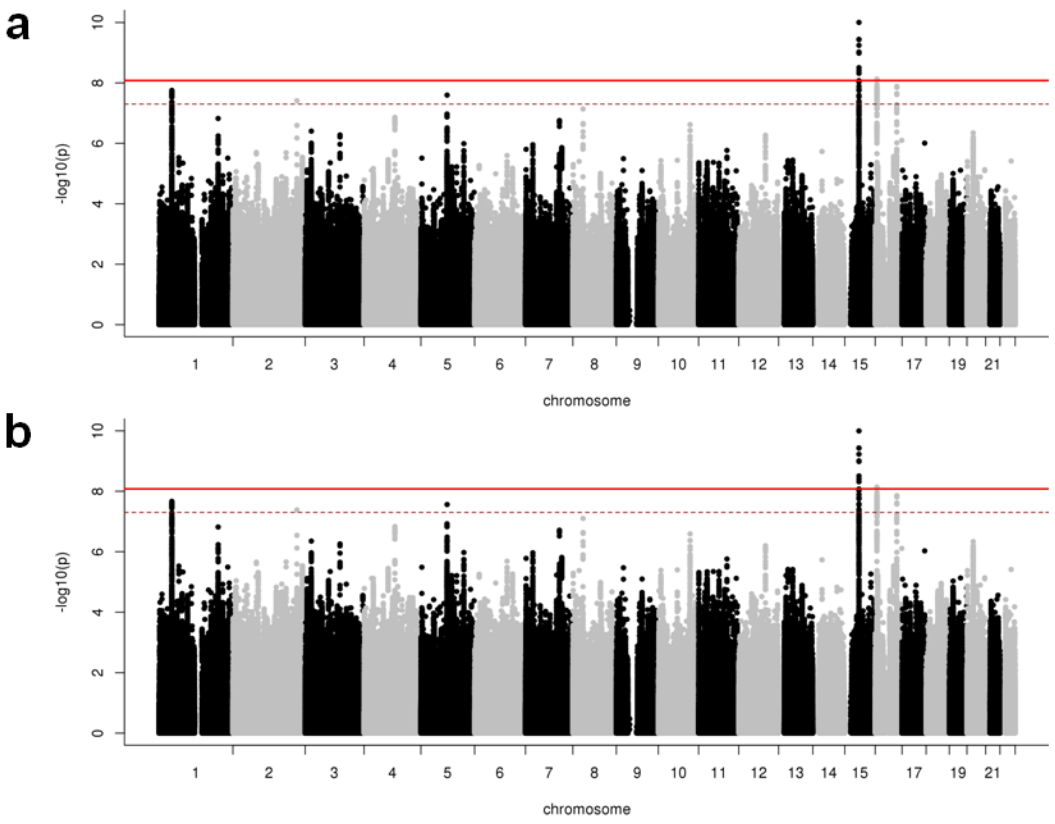

FIGURE S10. Common genetic variants associated with ADHD+ICV. Shown here are Manhattan plots, in which every point represents a single genetic variant plotted according to its genomic position (x-axis) and its $-\log_{10}(P)$ for association with the respective trait (y-axis). The solid bright red line represents the threshold for study-wide genome-wide significance at $P=8.33\times10^{-9}$, and the dashed dark red line represents the threshold for genome-wide significance at $P=5\times10^{-8}$. (**a**) ADHD+ICV weighted GWAS-MA. (**b**) ADHD+ICV naïve (without additional weight factors) GWAS-MA.

SUPPLEMENTARY TABLES

TABLE S1. Sample characteristics of the different cohorts used in this study.

Cohort	Trait	$N_{subjects}$	$N_{genetic\ variants}$	Reference
PGC-iPSYCH	ADHD	20,183 cases/ 35,191 controls	8,047,420	(1)
ENIGMA only*	Nucleus accumbens volume	11,709	8,615,659	(4)
	Amygdala volume	11,757	8,601,199	
	Caudate nucleus volume	11,772	8,615,485	
	Hippocampus volume	11,665	8,610,806	
	Putamen volume	11,646	8,609,826	
	Intracranial volume	11,221	8,720,403	
CHARGE	Hippocampus volume	13,039	12,438,667	(9, 10)
	Intracranial volume	12,803	12,460,951	
MA ENIGMA*+CHARGE	Hippocampus volume	24,704	9,145,464	This manuscript
	Intracranial volume	24,024	9,186,920	

$N_{subjects}$=number of subjects included in this study after quality control; $N_{genetic\ variants}$=number of genetic variants available for this study after quality control. *ADHD cases from the NeuroIMAGE cohort (n=154) have been removed from this ENIGMA data set.

TABLE S2. SNP heritability analyses for MRI brain volumes and genetic correlation with ADHD using constrained intercepts*.

Brain region	N	Heritability	SE	Genetic correlation with ADHD	SE	Z	P
Nucleus accumbens	11,709	0.0477	0.0315	0.144	0.1027	1.403	0.1606
Caudate nucleus	11,772	0.1714	0.0322	0.04699	0.05531	0.8495	0.3956
Hippocampus#	24,704	0.1412	0.0186	-0.01677	0.04085	-0.4104	0.6815
Intracranial volume#	24,024	0.2873	0.0229	-0.2066	0.03247	-6.363	**$1.98x10^{-10}$**
Putamen	11,646	0.1736	0.0348	0.04018	0.05257	0.7643	0.4447
Hippocampus ENIGMA only	11,665	0.1318	0.0305	-0.03867	0.05958	-0.6491	0.5163
Intracranial volume ENIGMA only	11,221	0.1809	0.0307	-0.2117	0.0555	-3.814	**0.000137**

*Amygdala mean χ^2 was too small to allow a valid analysis (N=11,757). #Using GWAS-MA summary statistics from the meta-analysis of ENIGMA and CHARGE cohorts. Heritability and genetic correlation were estimated by using constrained intercepts. P-values in bold are significant after Bonferroni correction.

TABLE S3. Sign test results in brain volume cohorts.

P threshold	Brain region	N opposite direction	Proportion	P
$< 5x10^{-8}$	Nucleus accumbens	4	0.40	0.828
	Amygdala	6	0.60	0.377
	Caudate nucleus	4	0.40	0.828
	Hippocampus	4	0.40	0.828
	Intracranial volume	2	0.20	0.989
	Putamen	1	0.10	0.999
$< 1x10^{-6}$	Nucleus accumbens	14	0.40	0.912
	Amygdala	18	0.51	0.5
	Caudate nucleus	11	0.31	0.992
	Hippocampus	20	0.57	0.249
	Intracranial volume	17	0.49	0.632
	Putamen	12	0.34	0.979
$< 1x10^{-5}$	Nucleus accumbens	48	0.49	0.619
	Amygdala	52	0.53	0.307
	Caudate nucleus	38	0.39	0.990
	Hippocampus	57	0.58	0.065
	Intracranial volume	56	0.57	0.094
	Putamen	48	0.49	0.619
$< 5x10^{-8}$	Hippocampus ENIGMA only	6	0.60	0.377
	Intracranial volume ENIGMA only	3	0.33	0.910
$< 1x10^{-6}$	Hippocampus ENIGMA only	17	0.49	0.632
	Intracranial volume ENIGMA only	19	0.56	0.924
$< 1x10^{-5}$	Hippocampus ENIGMA only	50	0.51	0.459
	Intracranial volume ENIGMA only	50	0.51	0.419

Test of whether the proportion of index SNPs with estimated effects in the *opposite* direction as the ADHD GWAS-MA is greater than expected by chance. The expected proportion under the null hypothesis is 0.5. At threshold $P<5x10^{-8}$ 4 index SNPs were not available in the brain volume GWAS-MA data, so were 9 at threshold $P<5x10^{-6}$ and 34 at threshold $P<5x10^{-5}$. We set a Bonferroni-corrected significance level at P=0.05/(3*6)=0.0027.

TABLE S4. Sign test results for the intelligence GWAS-MA summary statistics from(14).

P threshold	Trait	Expected directionality	N SNPs included	N expected direction	Proportion	P
$< 1x10^{-5}$	ADHD+ICV	concordant	43	13	0.3023256	0.9973
		discordant	43	30	0.6976744	0.006859*
	ADHD	discordant	45	15	0.3333	0.992
	ICV	concordant	58	19	0.3275862	0.9973
$< 1x10^{-4}$	ADHD+ICV	concordant	225	96	0.4266667	0.9884
		discordant	225	129	0.5733333	0.01633
	ADHD	discordant	234	133	0.5683761	0.02124
	ICV	concordant	289	120	0.4152249	0.9984

Test of whether the proportion of index SNPs with estimated effects in the *same* (concordant) or *opposite* (discordant) direction as the ADHD GWAS-MA is greater than expected by chance. This test was done for LD-independent SNPs, which (1) passed the p-value threshold of $P<1x10^{-5}$ or $P<1x10^{-4}$ in the ADHD+ICV GWAS-MA and (2) showed smaller p-value in the ADHD+ICV GWAS-MA compared to the ADHD and ICV GWAS-MA individually. The expected proportion under the null hypothesis is 0.5. We set a Bonferroni-corrected significance level at P=0.05/(2*3)=0.00833; significant results are indicated by an asterisk(*).

TABLE S5. Results of MAGMA gene-based associations of all genes for ADHD and amygdala volume.

>>> see Excel file *appi.ajp.2019.18020149.ds003_Table_S5.xlsx* <<<

Genome-wide gene-based results of MAGMA (15) analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA amygdala GWAS-MA (tab 2), and the weighted ADHD+amygdala GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731x10^{-6}$; genes marked in bold).

TABLE S6. Results of MAGMA gene-based associations of all genes for ADHD and nucleus accumbens volume.

>>> see file *appi.ajp.2019.18020149.ds004_Table_S6.xlsx* <<<

Genome-wide gene-based results of MAGMA (15) analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA nucleus accumbens GWAS-MA (tab 2), and the weighted ADHD+nucleus accumbens GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731x10^{-6}$; genes marked in bold).

TABLE S7. Results of MAGMA gene-based associations of all genes for ADHD and caudate nucleus volume.

>>> see file *appi.ajp.2019.18020149.ds005_Table_S7.xlsx* <<<

Genome-wide gene-based results of MAGMA (15) analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA caudate nucleus GWAS-MA (tab 2), and the weighted ADHD+caudate nucleus GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731x10^{-6}$; genes marked in bold).

TABLE S8. Results of MAGMA gene-based associations of all genes for ADHD and hippocampus volume.

>>> see file *appi.ajp.2019.18020149.ds006_Table_S8.xlsx* <<<

Genome-wide gene-based results of MAGMA (15) analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA+CHARGE hippocampus GWAS-MA (tab 2), and the weighted ADHD+hippocampus GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731x10^{-6}$; genes marked in bold).

TABLE S9. Results of MAGMA gene-based associations of all genes for ADHD and putamen volume.

>>> see file *appi.ajp.2019.18020149.ds007_Table_S9.xlsx* <<<

Genome-wide gene-based results of MAGMA (15) analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA putamen GWAS-MA (tab 2), and the weighted ADHD+putamen GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731x10^{-6}$; genes marked in bold).

TABLE S10. Results of MAGMA gene-based associations of all genes for ADHD and ICV.

>>> see file *appi.ajp.2019.18020149.ds008_Table_S10.xlsx* <<<

Genome-wide gene-based results of MAGMA (15) analysis. Entrez-ID (GENE), Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), effective number of SNPs included (NPARAM), the total sample size (N), test statistics (ZSTAT), and gene-based p-values for ADHD GWAS-MA (tab 1), ENIGMA+CHARGE ICV GWAS-MA (tab 2), and the weighted ADHD+ICV GWAS-MA (tab 3) are shown. Genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the total number of genes (N=18,306; $P<2.731x10^{-6}$; genes marked in bold).

TABLE S11. Comparison of genome-wide significant MAGMA gene-based results for ADHD and ICV.

Gene Name	EntrezID	P_{ADHD}	P_{ICV}	$P_{ADHD+ICV}$
SEMA6D	80031	$3.48x10^{-09}$	0.002926	**$1.84x10^{-12}$**
MEF2C	4208	$5.99x10^{-10}$	0.001512	**$2.49x10^{-10}$**
PTPRF	5792	$1.23x10^{-13}$	0.55807	$7.37x10^{-09}$
SZT2	23334	$1.26x10^{-12}$	0.81234	$1.41x10^{-08}$
KIZ	55857	$6.47x10^{-07}$	0.015378	**$1.48x10^{-08}$**
DUSP6	1848	$4.53x10^{-11}$	0.73979	$4.73x10^{-08}$
HYI	81888	$3.28x10^{-12}$	0.74378	$8.07x10^{-08}$
KDM4A	9682	$4.07x10^{-12}$	0.348	$8.10x10^{-08}$
CDC20	991	$1.52x10^{-10}$	0.7465	$1.73x10^{-07}$
ELOVL1	64834	$1.68x10^{-10}$	0.74685	$1.96x10^{-07}$
MPL	4352	$1.84x10^{-09}$	0.62443	$4.45x10^{-07}$
MED8	112950	$2.39x10^{-10}$	0.73188	$7.98x10^{-07}$
TIE1	7075	$1.11x10^{-08}$	0.72988	$1.42x10^{-06}$
ST3GAL3	6487	$2.76x10^{-14}$	0.068167	$1.50x10^{-06}$
RUNX1T1	862	$1.28x10^{-06}$	0.43967	$2.05x10^{-06}$
FOXP2	93986	$3.50x10^{-07}$	0.51984	$2.67x10^{-06}$

Genome-wide significant gene-based results of MAGMA (15) for the 16 genes overlapping between the ADHD and ADHD+ICV data sets. Three genes showed stronger association (smaller cross-trait p-value and nominally significant p-value (P<0.05) in ICV data set, marked in bold) in the cross-trait meta-analysis compared to the separate analyses of ADHD and ICV.

TABLE S12. Comparison of genome-wide significant MAGMA gene-based results for ADHD and amygdala volume.

Gene name	EntrezID	P_{ADHD}	$P_{amygdala}$	$P_{ADHD+amygdala}$
ST3GAL3	6487	2.76E-14	0.25993	2.42E-13
PTPRF	5792	1.23E-13	0.23627	3.68E-13
SZT2	23334	1.26E-12	0.85979	1.79E-12
KDM4A	9682	4.07E-12	0.094323	1.09E-11
HYI	81888	3.28E-12	0.83715	1.24E-11
DUSP6	1848	4.53E-11	0.54697	2.54E-11
MEF2C	4208	5.99E-10	0.61052	1.43E-10
ELOVL1	64834	1.68E-10	0.83649	1.68E-10
CDC20	991	1.52E-10	0.83847	1.92E-10
MPL	4352	1.84E-09	0.82465	5.30E-10
MED8	112950	2.39E-10	0.82975	9.47E-10
SEMA6D	80031	3.48E-09	0.59009	4.69E-09
SORCS3	22986	1.64E-08	0.26674	5.55E-09
TIE1	7075	1.11E-08	0.65502	1.39E-08
ARTN	9048	5.38E-08	0.72927	2.33E-08
IPO13	9670	3.79E-08	0.87871	4.50E-08
CDH8	1006	4.93E-08	0.17713	1.05E-07
FEZF1	389549	6.00E-07	0.017209	**1.35E-07**
C1ORF210	149466	1.97E-07	0.59275	1.44E-07
FOXP2	93986	3.50E-07	0.75094	2.31E-07
DPH2	1802	1.02E-07	0.89686	2.35E-07
MANBA	4126	2.26E-07	0.26696	2.54E-07
ATP6V0B	533	2.43E-07	0.91025	4.52E-07
TMEM125	128218	5.82E-07	0.48427	6.64E-07
B4GALT2	8704	4.38E-07	0.89299	7.37E-07
KIZ	55857	6.47E-07	0.2255	7.65E-07
POC1B	282809	1.09E-06	0.75771	9.53E-07
ADD1	118	1.24E-06	0.83043	1.07E-06
RUNX1T1	862	1.28E-06	0.041461	1.41E-06

Genome-wide significant gene-based results of MAGMA (15) for the 29 genes overlapping between the ADHD and ADHD+amygdala data sets. One gene showed stronger association (smaller cross-trait p-value and nominally significant p-value (P<0.05) in amygdala data set, marked in bold) in the cross-trait meta-analysis compared to the separate analyses of ADHD and amygdala.

TABLE S13. Comparison of genome-wide significant MAGMA gene-based results for ADHD and nucleus accumbens volume.

Gene name	EntrezID	P_{ADHD}	$P_{accumbens}$	$P_{ADHD+accumbens}$
ST3GAL3	6487	2.755E-14	0.94551	5.5663E-13
PTPRF	5792	1.2327E-13	0.94222	7.5999E-13
SZT2	23334	1.2552E-12	0.87531	3.945E-12
DUSP6	1848	4.5262E-11	0.43645	1.4698E-11
KDM4A	9682	4.0725E-12	0.96018	1.7656E-11
HYI	81888	3.2804E-12	0.86699	2.7053E-11
MEF2C	4208	5.9876E-10	0.63371	1.6309E-10
ELOVL1	64834	1.6783E-10	0.8459	3.5548E-10
CDC20	991	1.5191E-10	0.83473	4.1098E-10
MPL	4352	1.8383E-09	0.74892	1.306E-09
SEMA6D	80031	3.4794E-09	0.26938	1.6221E-09
MED8	112950	2.389E-10	0.90161	1.7026E-09
TIE1	7075	1.1146E-08	0.36207	1.7039E-08
SORCS3	22986	1.6383E-08	0.22952	2.2168E-08
FOXP2	93986	3.5042E-07	0.39951	4.1417E-08
CDH8	1006	4.9347E-08	0.74346	4.5358E-08
ARTN	9048	5.3775E-08	0.76902	4.7319E-08
IPO13	9670	3.7875E-08	0.6043	7.4177E-08
FEZF1	389549	6.0003E-07	0.66124	9.5065E-08
C1ORF210	149466	1.9719E-07	0.27701	1.8071E-07
DPH2	1802	1.016E-07	0.60244	3.1423E-07
TMEM125	128218	5.8163E-07	0.17473	6.1746E-07
ATP6V0B	533	2.4309E-07	0.56608	6.2568E-07
MANBA	4126	2.2558E-07	0.89609	6.4895E-07
ADD1	118	1.2405E-06	0.30503	9.2319E-07
B4GALT2	8704	4.3771E-07	0.52686	1.0343E-06
KIZ	55857	6.4723E-07	0.91178	1.1743E-06
POC1B	282809	1.0927E-06	0.2469	1.4311E-06
LRFN2	57497	2.5802E-06	0.10434	1.8371E-06
CEND1	51286	2.4283E-06	0.85151	2.1283E-06

Genome-wide significant gene-based results of MAGMA (15) for the 30 genes overlapping between the ADHD and ADHD+nucleus accumbens data sets. No gene showed stronger association (smaller cross-trait p-value and nominally significant p-value ($P<0.05$) in nucleus accumbens data set) in the cross-trait meta-analysis compared to the separate analyses of ADHD and nucleus accumbens.

TABLE S14. Comparison of genome-wide significant MAGMA gene-based results for ADHD and caudate nucleus volume.

Gene name	EntrezID	P_{ADHD}	$P_{caudate}$	$P_{ADHD+acaudate}$
ST3GAL3	6487	2.755E-14	0.88846	1.84E-12
PTPRF	5792	1.2327E-13	0.88716	3.3722E-12
SZT2	23334	1.2552E-12	0.93397	1.3417E-11
DUSP6	1848	4.5262E-11	0.42831	2.599E-11
MEF2C	4208	5.9876E-10	0.067713	4.1061E-11
KDM4A	9682	4.0725E-12	0.64592	4.1825E-11
HYI	81888	3.2804E-12	0.94235	8.2796E-11
ELOVL1	64834	1.6783E-10	0.85376	1.2399E-09
CDC20	991	1.5191E-10	0.85221	1.5244E-09
MED8	112950	2.389E-10	0.85312	3.7897E-09
MPL	4352	1.8383E-09	0.85695	7.2054E-09
CDH8	1006	4.9347E-08	0.47936	3.2218E-08
FEZF1	389549	6.0003E-07	0.10085	3.9442E-08
TIE1	7075	1.1146E-08	0.65191	9.637E-08
SORCS3	22986	1.6383E-08	0.80094	9.6541E-08
FOXP2	93986	3.5042E-07	0.47231	1.2157E-07
ARTN	9048	5.3775E-08	0.98566	1.9172E-07
ADD1	118	1.2405E-06	0.0162	**4.586E-07**
IPO13	9670	3.7875E-08	0.96342	4.721E-07
SEMA6D	80031	3.4794E-09	0.22968	7.0042E-07
C1ORF210	149466	1.9719E-07	0.5263	8.9503E-07
RUNX1T1	862	0.000001283	0.43918	1.0648E-06
POC1B	282809	1.0927E-06	0.45431	1.2555E-06
DPH2	1802	1.016E-07	0.93774	0.000002359
TMEM125	128218	5.8163E-07	0.33768	0.000002393

Genome-wide significant gene-based results of MAGMA (15) for the 25 genes overlapping between the ADHD and ADHD+caudate nucleus data sets. One gene showed stronger association (smaller cross-trait p-value and nominally significant p-value ($P<0.05$) in caudate nucleus data set, marked in bold) in the cross-trait meta-analysis compared to the separate analyses of ADHD and caudate nucleus.

TABLE S15. Comparison of genome-wide significant MAGMA gene-based results for ADHD and hippocampus volume.

Gene name	EntrezID	P_{ADHD}	$P_{hippocampus}$	$P_{ADHD+hippocampus}$
ST3GAL3	6487	2.76E-14	0.61499	2.49E-13
PTPRF	5792	1.23E-13	0.49516	3.85E-13
KDM4A	9682	4.07E-12	0.43352	3.85E-12
SZT2	23334	1.26E-12	0.70324	2.86E-11
HYI	81888	3.28E-12	0.59579	1.05E-10
MANBA	4126	2.26E-07	0.000875	**1.00E-09**
CDC20	991	1.52E-10	0.87975	5.25E-09
ELOVL1	64834	1.68E-10	0.88041	5.74E-09
SORCS3	22986	1.64E-08	0.41568	6.88E-09
MED8	112950	2.39E-10	0.84623	1.84E-08
IPO13	9670	3.79E-08	0.58968	1.98E-08
MPL	4352	1.84E-09	0.9076	2.76E-08
ARTN	9048	5.38E-08	0.66681	5.47E-08
DUSP6	1848	4.53E-11	0.43039	6.12E-08
TIE1	7075	1.11E-08	0.87312	1.31E-07
DPH2	1802	1.02E-07	0.34401	1.45E-07
SEMA6D	80031	3.48E-09	0.98523	1.84E-07
LRFN2	57497	2.58E-06	0.078658	1.95E-07
CDH8	1006	4.93E-08	0.40683	2.36E-07
ATP6V0B	533	2.43E-07	0.22951	3.45E-07
B4GALT2	8704	4.38E-07	0.32276	6.51E-07
C1ORF210	149466	1.97E-07	0.8807	9.91E-07
MEF2C	4208	5.99E-10	0.007951	1.14E-06
KIZ	55857	6.47E-07	0.5552	1.44E-06

Genome-wide significant gene-based results of MAGMA (15) for the 24 genes overlapping between the ADHD and ADHD+hippocampus data sets. One gene showed stronger association (smaller cross-trait p-value and nominally significant p-value ($P<0.05$) in caudate nucleus data set, marked in bold) in the cross-trait meta-analysis compared to the separate analyses of ADHD and caudate nucleus.

TABLE S16. Comparison of genome-wide significant MAGMA gene-based results for ADHD and putamen volume.

Gene name	EntrezID	P_{ADHD}	$P_{putamen}$	$P_{ADHD+putamen}$
ST3GAL3	6487	2.76E-14	0.36927	9.37E-14
PTPRF	5792	1.23E-13	0.59089	5.08E-13
KDM4A	9682	4.07E-12	0.32362	6.64E-12
SZT2	23334	1.26E-12	0.91611	7.26E-12
HYI	81888	3.28E-12	0.92929	5.01E-11
MEF2C	4208	5.99E-10	0.49053	5.38E-11
DUSP6	1848	4.53E-11	0.72256	8.57E-11
ELOVL1	64834	1.68E-10	0.8585	5.58E-10
CDC20	991	1.52E-10	0.85348	6.71E-10
SEMA6D	80031	3.48E-09	0.11999	1.31E-09
MED8	112950	2.39E-10	0.9054	2.39E-09
MPL	4352	1.84E-09	0.79741	2.57E-09
ARTN	9048	5.38E-08	0.52654	1.54E-08
IPO13	9670	3.79E-08	0.57582	3.37E-08
TIE1	7075	1.11E-08	0.73736	3.78E-08
SORCS3	22986	1.64E-08	0.57283	1.11E-07
KIZ	55857	6.47E-07	0.14818	1.53E-07
DPH2	1802	1.02E-07	0.62207	1.95E-07
C1ORF210	149466	1.97E-07	0.60083	3.05E-07
ATP6V0B	533	2.43E-07	0.64662	4.13E-07
FOXP2	93986	3.50E-07	0.61062	5.67E-07
FEZF1	389549	6.00E-07	0.72766	6.20E-07
B4GALT2	8704	4.38E-07	0.65805	6.86E-07
RUNX1T1	862	1.28E-06	0.62215	9.28E-07
TMEM125	128218	5.82E-07	0.56387	1.24E-06
CEND1	51286	2.43E-06	0.24057	2.65E-06

Genome-wide significant gene-based results of MAGMA (15) for the 26 genes overlapping between the ADHD and ADHD+putamen data sets. No gene showed stronger association (smaller cross-trait p-value and nominally significant p-value ($P<0.05$) in putamen data set) in the cross-trait meta-analysis compared to the separate analyses of ADHD and putamen.

TABLE S17. Reciprocal look-up of significantly associated ADHD index SNPs in brain volume GWAS data.

>>> see file *appi.ajp.2019.18020149.ds009_Table_S17.xlsx* <<<

GWAS results from brain volume GWASs for the genome-wide significant loci identified in the ADHD GWAS. Replication is tested for the index variant from the ADHD GWAS, or for a proxy variant when the index variant is not present in the brain volume cohorts. Effects (Z-score or odds ratio [OR] with reference to allele 1 [A1]) that are sign concordant with the ADHD GWAS are indicated in bold.

TABLE S18. Reciprocal look-up of significantly associated brain volume index SNPs in ADHD GWAS data.

Brain trait	Index SNP	A1	A2	chr	pos	$Zscore_{brain}$	P_{brain}	Proxy	LD to index (r2)	OR_{ADHD}	P_{ADHD}
Caudate nucleus[a]	rs1318862	T	C	11	92007101	5.468	$4.56x10^{-8}$	/	/	0.98255	0.1971
Hippocampus [b]	rs77956314	T	C	12	117323367	-9.530	$1.63 x10^{-21}$	/	/	**0.97307**	0.2692
	rs61921502	T	G	12	65832468	8.743	$2.26 x10^{-18}$	/	/	0.97346	0.1769
	rs11979341	C	G	7	155797978	-6.523	$6.90 x10^{-11}$	rs4716969	0.352	**0.98847**	0.5723
	rs7020341	C	G	9	119247974	6.704	$2.03 x10^{-11}$	/	/	**1.03179**	0.02228
	rs2268894	T	C	2	162856148	-7.231	$4.78 x10^{-13}$	/	/	**0.99035**	0.4634
	rs2289881	T	G	5	66084260	-5.245	$1.56 x10^{-7}$	/	/	1.0015	0.9144
Putamen[a]	rs945270	C	G	14	56200473	9.237	$2.54 x10^{-20}$	/	/	0.98728	0.3432
	rs62097986	A	C	18	50818827	6.348	$2.18 x10^{-10}$	/	/	**1.03252**	0.01785
	rs6087771	T	C	20	30306724	5.624	$1.87 x10^{-8}$	/	/	0.98501	0.3109
	rs683250	A	G	11	83276168	-5.081	$3.75 x10^{-7}$	/	/	**0.99084**	0.5009
Intracranial volume [b]	rs199525	T	G	17	44847834	9.262	$2.00 x10^{-20}$	/	/	0.9659	0.04306
	rs11759026	A	G	6	126792095	-8.793	$1.45 x10^{-18}$	/	/	1.03087	0.06001
	rs2022464	A	C	6	108945370	-6.418	$1.38 x10^{-10}$	/	/	**0.97893**	0.1454
	rs11191683	T	G	10	105170649	6.046	$1.49 x10^{-9}$	/	/	0.98955	0.4545
	rs9811910	C	G	3	190670902	5.988	$2.12 x10^{-9}$	/	/	0.98187	0.425
	rs138074335	A	G	12	66374247	5.694	$1.24 x10^{-8}$	rs8756	1	**1.04227**	**0.001863**
	rs2195243	C	G	12	102922986	-5.260	$1.44 x10^{-7}$	/	/	1.05654	**0.001267**
Hippocampus ENIGMA only[a]	rs77956314	T	C	12	117323367	-5.626	$1.84 x10^{-8}$	/	/	**0.97307**	0.2692
	rs61921502	T	G	12	65832468	5.7331	$9.89 x10^{-9}$	/	/	0.97346	0.1769
Intracranial volume ENIGMA only[a]	rs17689882	A	G	17	43906828	-5.939	$2.85 x10^{-9}$	/	/	1.0453	0.008742

GWAS results from ADHD GWAS for the genome-wide significant loci identified in the different brain volume GWASs. Those SNPs were selected from the original publications(4, 9, 10). Replication is tested for the index variant from the brain volume GWASs, or for a proxy variant when the index variant is not present in the brain volume cohorts. Effects (Z-score or odds ratio [OR] with reference to allele 1 [A1]) that are sign concordant with the brain volume GWASs are indicated in bold. P-values in bold are significant after Bonferroni correction for testing 21 variants (P<0.00238). A proxy variant (rs8756; r^2=1; chr12:66359752, located in exon 5 of *HMGA2*) of the ICV-associated variant rs138074335 (chr12:66374247, intergenic and upstream of *HMGA2*; increasing ICV) was associated with increased risk for ADHD (OR=1.042, P=0.00186). A second variant, rs2195243 (chr12:102922986, intergenic and upstream of *IGF1*), was associated with decreased ICV and increased risk for ADHD (OR=1.0565, P=0.00127). [a] Z-scores and corresponding P-values were retrieved from the ENIGMA only brain volume GWAS-MA data excluding ADHD cases. [b] Z-scores and corresponding P-values were retrieved from the ENGIMA2(without ADHD) and CHARGE meta-analysis described in this study.

TABLE S19. Single tissue eQTL results for index SNPs of relevant genome-wide significant loci in the ADHD+brain volume meta-analyses.

		Index SNP				
		rs281320	**rs281323**	**rs12653396**	**rs8756**	**rs2195243**
Tissue (N)	**Gene**	*SEMA6D*	*SEMA6D*	*CTC-498M16.4*	*HMGA2*	*CCDC53*
Cells - Transformed fibroblasts (300)	P	$1.7x10^{-20}$	$7.4 x10^{-24}$	---	$9.8x10^{-6}$	$4.8 x10^{-3}$
	NES	0.52	0.55	---	-0.134	-0.132
Amygdala (88)	P	0.8	0.9	$4.5x10^{-7}$	---	0.8
	NES	-0.0215	-0.0162	-0.543	---	0.0248
Caudate (144)	P	0.6	0.5	$1.8x10^{-4}$	---	0.2
	NES	-0.0371	-0.0397	-0.339	---	0.127
Hippocampus (111)	P	0.5	0.5	$7.4x10^{-9}$	---	0.3
	NES	0.0507	0.0509	-0.605	---	0.0951
Nucleus accumbens (130)	P	0.2	0.1	$8.6x10^{-9}$	---	0.1
	NES	0.0892	0.108	-0.466	---	0.169
Putamen (111)	P	0.6	0.3	$5.6x10^{-6}$	---	0.9
	NES	0.0339	0.0817	-0.406	---	0.0188
Cortex (136)	P	0.1	0.1	$3.2x10^{-6}$	---	1
	NES	0.133	0.141	-0.451	---	0.00248
Frontal Cortex (118)	P	0.6	0.2	$4.4x10^{-7}$	---	0.7
	NES	0.0417	0.109	-0.524	---	-0.0396
Blood (5,311)	P	---	---	$6.53x10^{-7}$ *	---	---
	Z-score	---	---	-4.97	---	---

All six index SNPs from the weighted ADHD+brain volume meta-analyses with a $P<8.33x10^{-9}$ and the two significant variants from the reciprocal lookup of genome-wide significant associations were included in the eQTL analysis. All SNPs with available data in the GTEx portal (18) and the blood eQTL browser (19) are shown above. Only variant rs12653396 was present in both the GTEx portal and blood eQTL browser. N=sample size. NES=normalized effect size. *cis-eQTL for *MEF2C.*

TABLE S20. Results of MAGMA gene-set analyses results for the neurite outgrowth gene-set.

GWAS-MA	NGENES	BETA	BETA_STD	SE	COMP_P	SELF_P
ADHD+Intracranial volume	45	0.367	0.0182	0.136	**0.00338**	**$1.55x10^{-6}$**
ADHD	45	0.148	0.0073	0.145	0.15391	**$5.53x10^{-9}$**
Intracranial volume	45	-0.0785	-0.00389	0.14	0.71179	0.40748

Competitive (COMP_P) and self-contained (SELF_P) results of the gene-set analysis of the neurite outgrowth gene-set performed using MAGMA (15). The number of genes (N GENES), raw and semi-standardized (STD) regression coefficients, and corresponding standard error (SE) are reported. Significant results after Bonferroni correction are shown in bold.

TABLE S21. Results of MAGMA gene-based associations of neurite outgrowth genes.

GENE_NAME	CHR	START	STOP	NSNPS	ZSTAT	$P_{ADHD+ICV}$	P_{ADHD}	P_{ICV}
CREB5	7	28238940	28965511	1822	3.2619	**0.000553**	0.0005475	0.074382
MMP24	20	33714539	33964804	453	2.5709	0.005071	0.0034001	0.77984
TLL2	10	98024363	98373683	898	2.4879	0.006425	0.033235	0.43003
NEDD4L	18	55611580	56168772	1607	2.3373	0.009711	0.0062839	0.86232
DNM1	9	130865634	131117528	389	2.293	0.010923	0.0014409	0.58186
ASTN2	9	119087504	120277317	3253	2.1668	0.015126	0.0001023	0.093386
NRXN1	2	50045643	51359674	3836	2.1233	0.016864	0.13173	0.33824
SUPT3H	6	44694467	45445788	2144	2.0192	0.021735	0.17377	0.066473
BMPR1B	4	95579128	96179601	1564	2.0112	0.022152	0.024176	0.82239
CSMD2	1	33879609	34731443	1845	1.77	0.038365	0.00806	0.16337
ADAMTS17	15	100411643	100982183	2451	1.4316	0.076131	0.059053	0.85152
ZNF423	16	49424515	49991830	1425	1.4178	0.078126	0.2668	0.20731
GPC6	13	93779078	95160274	3351	1.1491	0.12527	0.56497	0.016549
MYT1L	2	1692885	2435147	1924	1.1262	0.13004	0.022068	0.57042
MBOAT1	6	19999915	20312695	770	1.1239	0.13054	0.036503	0.58052
PPM1H	12	62937762	63428665	1293	1.1171	0.13197	0.24579	0.0385
EMP2	16	10522279	10774539	854	1.078	0.14052	0.10888	0.20062
MAP1B	5	71303118	71605397	630	1.0463	0.14772	0.056063	0.39159
UNC5B	10	72872292	73162635	776	0.8627	0.19415	0.27714	0.57631
NOS1	12	117545921	117899607	869	0.80518	0.21036	0.30687	0.11535
CDH13	16	82560399	83930215	7024	0.80402	0.21069	0.093966	0.91052
NUCB1	19	49303307	49526540	498	0.71	0.23885	0.071321	0.36184
SLCO3A1	15	92296938	92815665	1440	0.65899	0.25495	0.22741	0.35818
CDH23	10	73056691	73675704	1730	0.63549	0.26255	0.18278	0.98778
NXPH1	7	8373585	8892593	1664	0.53694	0.29565	0.0776	0.66363
KCNIP4	4	20630234	22050424	4489	0.40482	0.34281	0.41226	0.71094
MAN2A2	15	91347420	91565815	588	0.37292	0.3546	0.29083	0.15025
HKDC1	10	70880059	71127315	687	0.30449	0.38038	0.7865	0.25629
CTNNA2	2	79640060	80975993	3424	0.23372	0.4076	0.06039	0.44387
FAM190A	4	90948684	92623370	4371	0.14582	0.44203	0.053733	0.37609
FLNC	7	128370436	128599328	468	0.075226	0.47002	0.37628	0.79661
HK1	10	70929740	71261638	1025	0.061092	0.47564	0.51193	0.52288
KCP	7	128416919	128650773	446	-0.12722	0.55062	0.6579	0.79675
SPOCK3	4	167554535	168255741	1629	-0.14745	0.55861	0.51736	0.60259
DYNC2H1	11	102880160	103450591	2201	-0.31828	0.62487	0.78806	0.70885
FHIT	3	59635036	61337133	6164	-0.36753	0.64339	0.12672	0.8485
NCKAP5	2	133329361	134499118	2564	-0.37607	0.64657	0.17621	0.88675
DUSP1	5	172095093	172298203	605	-0.46873	0.68037	0.30004	0.72951
ATP2C2	16	84302129	84597793	1667	-0.48023	0.68447	0.85789	0.75574
MOBP	3	39409064	39670988	815	-0.67089	0.74885	0.83675	0.88765

ITGA11	15	68491128	68824502	751	-0.68035	0.75186	0.52294	0.37697
MEIS1	2	66562257	66899891	728	-0.96337	0.83232	0.77393	0.25917
RORA	15	60680483	61621502	2214	-1.0152	0.84501	0.81967	0.94611
UGT1A9	2	234480544	234781951	949	-1.2084	0.88654	0.30306	0.37333
LRP1B	2	140888996	142989270	7745	-1.3082	0.90461	0.91812	0.1159

MAGMA (15) gene-based analysis of previously reported neurite outgrowth candidate genes (16). Chromosome (CHR), Start (START) and end (STOP) position of the genes, number of SNPs in the genes (N SNPs), test statistics (ZSTAT), and gene-based p-values for 1) the weighted ADHD+ICV GWAS-MA ($\mathbf{P_{ADHD+ICV}}$), 2) ADHD GWAS-MA ($\mathbf{P_{ADHD}}$), and 3) ENIGMA+CHARGE ICV GWAS-MA ($\mathbf{P_{ICV}}$) are shown. For the results of the weighted ADHD+ICV GWAS-MA, genes were considered gene-wide significant, if they reached the Bonferroni correction threshold adjusted for the number of genes within the total gene-set (N=45; P<0.00111; genes marked in bold).

TABLE S22. Results for the 19 most strongly associated SNPs from the weighted ADHD+ICV GWAS-MA. Results for the naïve (non-weighted) GWAS-MA are shown in **$Zscore_{naive\ MA}$** and **$P_{naive\ MA}$**.

SNP	CHR	BP	$Zscore_{PGC}$	$Zscore_{ICV}$	$Zscore_{naive\ MA}$	$Zscore_{weighted\ MA}$	$P_{naive\ MA}$	$P_{weighted\ MA}$
rs281320	15	47769424	-5.54867	-3.33	-6.46553	-6.4677	$1.01x10^{-10}$	$9.95x10^{-11}$
rs8039398	15	47730870	-5.48151	-3.07	-6.26643	-6.27022	$3.69x10^{-10}$	$3.61x10^{-10}$
rs1656604	15	47794252	-5.36599	-3.243	-6.26511	-6.26704	$3.73x10^{-10}$	$3.68x10^{-10}$
rs281324	15	47754018	-5.5595	-2.817	-6.19239	-6.19846	$5.93x10^{-10}$	$5.70x10^{-10}$
rs281323	15	47754027	5.477548	2.796	6.112398	6.118231	$9.81x10^{-10}$	$9.46\ x10^{-10}$
rs1610098	15	47806012	-5.13664	-3.297	-6.10329	-6.10369	$1.04x10^{-9}$	$1.04x10^{-9}$
rs1612378	15	47813991	-4.94219	-3.269	-5.9255	-5.92516	$3.11x10^{-9}$	$3.12x10^{-9}$
rs1656622	15	47813909	-4.94219	-3.2	-5.88754	-5.88772	$3.92x10^{-9}$	$3.92x10^{-9}$
rs1347469	15	47814528	-4.93526	-3.147	-5.8526	-5.85314	$4.84x10^{-9}$	$4.82x10^{-9}$
rs13332522	16	5829204	4.616228	3.508	5.784743	5.781012	$7.26x10^{-9}$	$7.43x10^{-9}$
rs4597332	16	5829191	-4.61653	-3.499	-5.78004	-5.77638	$7.47x10^{-9}$	$7.63x10^{-9}$
rs4513101	16	5829196	4.602781	3.505	5.771863	5.768088	$7.84x10^{-9}$	$8.02x10^{-9}$
rs1656623	15	47815484	4.820448	3.153	5.760016	5.75995	$8.41x10^{-9}$	$8.41x10^{-9}$
rs1618196	15	47797832	-4.90586	-2.985	-5.73893	-5.74055	$9.53x10^{-9}$	$9.44x10^{-9}$
rs7198618	16	5829440	4.52717	3.519	5.71642	5.71217	$1.09x10^{-8}$	$1.12x10^{-8}$
rs1656618	15	47810363	4.746723	3.133	5.687446	5.687169	$1.29x10^{-8}$	$1.29x10^{-8}$
rs12596294	16	72587093	5.572012	1.849	5.673685	5.686953	$1.40x10^{-8}$	$1.29x10^{-8}$
rs11861310	16	5835841	4.595736	3.348	5.679619	5.676988	$1.35x10^{-8}$	$1.37x10^{-8}$
rs212178	16	72578131	-5.76998	-1.515	-5.65614	-5.67288	$1.55x10^{-8}$	$1.40x10^{-8}$

TABLE S23. Overview of metadata for all individual traits and meta-analyzed summary statistics.

	ADHD	ICV*	Amygdala	Accumbens	Caudate	Hippocampus*	Putamen	ADHD+ICV*	ADHD+Amygdala	ADHD+Accumbens	ADHD+caudate	ADHD+hippocampus*	ADHD+putamen
Total Observed scale h2 (se)	0.234 (0.0154)	0.2348 (0.0313)	-0.0172 (0.0397)	0.1349 (0.0504)	0.2469 (0.0459)	0.1368 (0.027)	0.2922 (0.0555)	0.1112 (0.0089)	0.1883 (0.0124)	0.1827 (0.0121)	0.17 (0.0115)	0.1366 (0.0099)	0.1724 (0.0121)
Lambda GC	1.2531	1.1082	0.9986	1.0075	1.0345	1.0588	1.0345	1.1876	1.2498	1.2498	1.2332	1.2234	1.2365
Mean Chi^2	1.2973	1.1416	1.0003	1.0122	1.0415	1.0736	1.0436	1.2132	1.2973	1.2914	1.2733	1.2576	1.2745
Intercept (se)	1.0363 (0.0102)	1.0231 (0.01)	1.0046 (0.0067)	0.9785 (0.0083)	0.9818 (0.0074)	1.0024 (0.0091)	0.9719 (0.0086)	1.0284 (0.0094)	1.0333 (0.0103)	1.0344 (0.0102)	1.0351 (0.0098)	1.029 (0.0096)	1.0303 (0.0101)
Ratio (se)	0.1222 (0.0342)	0.1633 (0.0705)	14.0523 (20.3101)	< 0	< 0	0.0327 (0.1237)	< 0	0.1332 (0.044)	0.1119 (0.0345)	0.118 (0.0351)	0.1283 (0.0358)	0.1126 (0.0371)	0.1104 (0.0366)

*Using GWAS-MA summary statistics from the meta-analysis of ENIGMA and CHARGE cohorts. h2= SNP-based heritability. se= standard error. ICV= intracranial volume. A ratio < 0 usually indicates GC correction.

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