Other Supplementary Material
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Supplemental Materials:

Recruitment. Volunteers were recruited via mass mailings, using commercial mailing lists, to all families with children in the target age range within the geographic radius of 50 miles from the University. The mailing made clear that we were looking for children with possible or definite ADHD, as well as for healthy, typically developing children with no history of learning or attention problems. In response to mailings to parents of all children in the target age range in our catchment area, we received 2144 inquiries. (A response rate of about 1% for non-ADHD participants and about 30% for ADHD participants).

First Screen. An initial screening phone call served to establish eligibility (below) and interest. Nearly half were ruled out at this stage due to medications, other illnesses (e.g. autism), or lack of interest. Those who were excluded at this stage did not differ reliably from the final sample on sex ratio (p=.11) or non-white race (p=.22), but were marginally lower income (p=.06) and slightly younger (p=.06).

Second screen. For those remaining (n=1449), an in-person "diagnostic" visit was then scheduled. Here, a parent completed the Conners' Rating Scales-3rd Edition short form (1), Strengths and Difficulties Questionnaire long form including the impairment module (SDQ) (2), the ADHD Rating Scale ADHD-RS (3), and a semi-structured clinical interview administered by a Master's-degree level clinician Kiddie Schedule for Affective Disorders and Schizophrenia (4). Children completed a brief unstructured clinical interview with the same clinician, and with a psychometrician (BA-level staff or volunteer) completed a three-subtest short form of the WISC-IV Vocabulary, Block Design, and Information (5,6), and the Word Reading and Numerical Operations subtests of the WIAT-II (7) to estimate IQ and academic progress. Interviewers and testers wrote detailed observational notes. Teachers were contacted and completed the Conners'-3, SDQ, and ADHD-RS.

All clinical interviewers were trained to reliability of kappa >.80 for all diagnoses on the KSADS to a master interviewer, and had videotapes viewed by a supervisor and reviewed periodically to prevent procedural drift. Psychometric testers were trained to an accuracy standard prior to beginning work and also had videotapes viewed periodically to prevent drift. Exclusions. Children were excluded at baseline if they were on non-stimulant psychotropic medications (see Disallowed Medications in Table S1). They were also excluded for: history of non-febrile seizure, head injury with loss of consciousness > 60 seconds, diagnosis of autism spectrum disorder or intellectual disability, or other major medical conditions. After the diagnostic team (Step 2), 103 withdrew due to lack of further interest (e.g., only wanted the diagnostic screen), and 496 were ruled out for the following reasons: excess teacher-parent rating discrepancy (situational problems; 35%), subthreshold symptom count (not control or ADHD, 17%), psychosis, mania, current severe depressive episode, Tourette's syndrome, or head injury (10%), autism (7%), other health condition (7%), ineligible medication (2%), IQ<80 (n=1), or multiple rule outs. Among the eligible children with ADHD, 35% were prescribed stimulant medications and needed to complete the washout, only slightly lower than rates in community surveys for pre-adolescent children (8,9).

Diagnostic Assignment using a Best Estimate procedure. All materials were scored and presented to a clinical diagnostic team comprising board certified child psychiatrist with over 25 years of experience and a licensed child neuropsychologist with over 10 years of experience. Blind to one another's ratings and to the subsequent genetic or cognitive test scores, they formed a diagnostic opinion based on all available information. Their agreement rate for all diagnoses discussed in this paper was satisfactory (ADHD, kappa=.88; ADHD subtype, k>.80,

all other disorders with at least 5% base rate, k>.68). Disagreements were conferenced and consensus reached. Cases where consensus was not readily achieved were excluded.

Using a best estimate procedure (10). DSM-IV diagnoses were made independently by each clinician. To count symptoms, the clinicians used the following rule: If both parent and teacher ratings exceeded T>=60 on at least one ADHD scale and both rated at least 3 symptoms as "often" or "very often" on the ADHD rating scale (or for parents, were counted present on the K-SADS), the "or" algorithm could be employed (11). When either informant fell below this mark, and clinicians judged that this was not explained by successful medication treatment during the school day, then the case was rejected as failing to meet the DSM requirement of substantial symptoms present in more than one setting. In addition, it was required that all other DSM criteria were met, including (a) impairment (identified on the KSAD by the clinician as well as on the SDQ Impairment section), (b) onset prior to age 7 (current at the time we began enrollment), (c) sustained impairing symptoms > 1 year, and (d) symptoms of ADHD were not better accounted for by comorbid conditions, trauma history, or other confounds. Both current and lifetime diagnoses were assigned; for the present report, all children in the ADHD group met current and lifetime diagnosis for ADHD.

Exclusion criteria. Children were excluded for disallowed medications (see Supplemental Table S1), history of seizures or head injury, parent-teacher rating discrepancy making diagnosis uncertain, psychosis, mania, current major depressive episode, Tourette's syndrome, autism, and IQ<80.

Handedness. All participants stated they were right handed. This was checked with the Edinburg handedness questionnaire administered to 584 participants (those in the present study plus others). Primarily right-handed was confirmed for 100% of the sample (however, a borderline score was reported for 1.7%).

Related individuals and Final Sample. The flow chart for participation eligibility is depicted in Supplemental Figure S1. It shows that after eligibility evaluation, MRI scans were attempted on 587 children, of whom 501 provided reliable data for initial ADHD group analysis. (Note, the first wave 1 scan was used whenever possible, if it failed QC checks, then the next available scan for that child was used. All analyses matched data to the age at the scan used in the analysis). As noted, 312 of these were genetically unrelated and of European ancestry.

Medication washout. Children who were prescribed stimulant medications completed the MRI scan after a stimulant medication washout period of >= 7 half-lives.

MRI acquisition and processing. Structural and functional data were acquired using a 3T Siemens Trio Tim equipped with a 12-channel head coil. One T1 weighted structural image (TR = 2300ms, TE = 3.58ms, FOV = 256 x 256, orientation = saggital, voxel size=1mm x 1 mm x 1.1mm slice thickness) was acquired. Resting state data was acquired in three 5-minute blocks using blood oxygen level-dependent (BOLD) contrast (TR = 2500ms, TE = 30ms, flip angle = 90^{o}, FOV = 240mm, in-plane resolution = 3.8mm x 3.8mm with a slice thickness of 3.8 mm).

MRI Motion Estimation. Motion estimation was conducted based on a procedure recently published by (12). For the procedure, BOLD data acquired after the structural scans was utilized as a best estimate of motion. Because participants (including this sample) tend to move at similar rates throughout a run (13), motion during the BOLD scans can be utilized as a best estimate of motion during structural scans. Here each BOLD frame (volume) is aligned to the first frame of the run through a series of rigid body transform matrices, T_i, where i indexes frame

and the reference frame is indexed by 0. Each transform is calculated by minimizing the registration error,

$$\varepsilon_i^2 = \langle \left(g I_0\left(T(\vec{x})\right) - I_i(\vec{x}) \right)^2 \rangle, \quad (1)$$

where $I(\vec{x})$ is the image intensity at locus $\vec{x}$ and g is a scalar factor that compensates for fluctuations in mean signal intensity, spatially averaged over the whole brain (angle brackets). Each transform is represented by a combination of rotations and displacements. Thus,

$$T_i = \begin{bmatrix} R_i & \vec{d}_i \\ 0 & 1 \end{bmatrix}, \quad (2)$$

where R_i is a 3 × 3 rotation matrix and $\vec{d}_i$ is 3 × 1 column vector of displacements (in mm). R_i is the product of three elementary rotations about the cardinal axes. Thus, $R_i = R_{i\propto} R_{i\beta} R_{i\gamma}$, where

$$R_{i\propto} = \begin{bmatrix} 1 & 1 & 0 \\ 0 & \cos \propto_i & -\sin \alpha_i \\ 0 & \sin \alpha_i & \cos \propto_i \end{bmatrix}, R_{i\beta} = \begin{bmatrix} \cos \beta_i & 0 & \sin \beta_i \\ 0 & 1 & 0 \\ -\sin \beta_i & 0 & \cos \beta_i \end{bmatrix}, R_{i\gamma} = \begin{bmatrix} \cos \gamma_i & -\sin \gamma_i & 0 \\ \sin \gamma_i & \cos \gamma_i & 0 \\ 0 & 0 & 1 \end{bmatrix}, \quad (3)$$

and all angles are expressed in radians. From here, the computation of frame-wise displacement (FD) ensues. Retrospective head motion correction generates a 6-parameter representation of the head trajectory, T_i, where i indexes frame. Instantaneous frame displacement (FD_i) is evaluated as the sum of frame-to-frame change over the 6 rigid body parameters. Thus,

$$FD_i = |\Delta d_{ix}| + |\Delta d_{iy}| + |\Delta d_{iz}| + r \cdot (|\Delta \alpha_i| + |\Delta \beta_i| + |\Delta \gamma_i|), \quad (4)$$

where $\Delta d_{ix} = d_{(i-1)x} - d_{ix}$, and similarly for the remaining parameters. We assign r = 50 mm, which approximates the mean distance from the cerebral cortex to the center of the head for a healthy child or adult. Since FD_i is evaluated by backwards differences, it is defined for all frames except the first. The average FD across all BOLD data is then used as our motion measurement in the analyses.

GWAS Processing. Salivary DNA samples were genotyped at the Stanley Center for Psychiatric Research (Broad Institute of MIT and Harvard, Cambridge, MA) using the PsychCHIP_v1-1 (N=603,132 SNPs), developed by Illumina, Inc (San Diego, CA) in collaboration with the Psychiatric Genomics Consortium (PGC). Quality control procedures were applied using the GWASTools (14,15). All individuals had genotyping rates > 98%. Single nucleotide polymorphisms (SNPs) were excluded if the call rate < 97%, Hardy-Weinberg Equilibrium deviation (p < 1x10-6), ambiguous strand information, or differential call rates between genotyping batches or ethnic groups. SNPs located in regions of suggestive copy number anomalies as calculated by B-allele frequency (GWASTools) were also removed. In addition, SNPs not included in the Illumina PsychArray manifest were excluded due to poor performance across populations (Illumina, Inc.). The final data set included 552,352 SNPs.

Cohort ancestry and relatedness was determined through an iterative process using PC-AiR (16) (Population) and PC-relate (RELATE) (17) using the Bioconductor package GENESIS (Conomos, GENESIS). Individuals with third-degree or closer relations were portioned so that only one member of each family was used in the analysis. The final data set included 656 unrelated participants. Ancestry components were determined using principal components analysis after relatedness estimation using the GENESIS package. Nongenotyped SNPs were imputed with IMPUTE2 (18) using 1000 genomes (1KG phase 3) as the reference panel (https://mathgen.stats.ox.ac.uk/impute/1000GP_Phase3.html). Autosomal chromosomes (N=537,976 SNPs) were preprocessed and phased using SHAPEIT (19). Variant positions and

alleles were checked against the reference panel and SNPs that were missing, or mismatches were removed (115543 SNPs). Imputation was done on 3Mb chunks with 1Mb buffers on either side. Genotype probabilities were converted to best-guess genotypes with genotype set to missing if the probability < 0.8. The final data after imputation included 16,284,035 SNPs.

Polygenic Score Computation. The polygenic risk score (PGS) was constructed using the European-ancestry PGC meta-analysis (20) as the discovery data set (19099 ADHD cases, 34194 controls). Only SNPs with INFO score (imputation quality) > 0.8 in both the PGC meta-analysis and our data were considered. SNPs were clumped based on $r^2 < 0.1$ using genotypes from European samples of the 1KG phase 3 using PLINK v1.9 (https://www.cog-genomics.org/plink2). SNP rs3952787, although correlated with another significant SNP, was kept in the LD clumped SNP list, since it was highlighted as a top result in the PGC meta-analysis. From this filtered (LD clumped) SNP list, SNPs with $p < 0.5$ were selected for the polygenic score computation (N=139934). The PGS was calculated for all subjects in the target data set by multiplying the number of risk alleles (0, 1, or 2) by the log(odds ratio) of that SNP in the discovery data set and averaging over all SNPs. The allelic scoring function (--score) in PLINK v1.9 was used for the PGS calculation.

A note on the p-value threshold used the select SNPs for the polygenic score computation: Not having a third sample to validate the effects of the chosen p-value threshold on the PRS, we chose to select a fairly conservative threshold ($p < 0.5$), which is backed-up by the literature. Wray et al. suggest that for discovery data sets where only a few genome-wide significant associations are found (as in our case) it is likely that including more SNPs in the PRS will improve predictive power (21). In previous work by the PGC, the amount of variation explained by a PRS has been shown to increase with p-value threshold and then plateau, with very little difference seen between p-value thresholds of p=0.1 and greater (see Extended Data Figure 5 in the Schizophrenia Working Group paper cited below) (22). We have previously shown that this same pattern holds in our cohort (23). Table S2 shows the correlations among ADHD diagnosis, total brain volume, and ADHD PRS created with various p-value thresholds.

Similar methods were used to construct polygenic scores based on the ENIGMA GWAS results (24) for each available brain volume measure: intracranial volume (ICV), accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus (cerebellum volume was not measured in the ENIGMA study). For these scores, risk alleles were weighted by the β value for each SNP, rather than a log(odds ratio). The individual polygenic scores for brain volumes were based on between 150157 (for accumbens) and 160300 (for ICV) total SNPs.

In addition, an ICV polygenic score was computed based on data from the combined ENIGMA+CHARGE meta-analysis (25). A total of 125481 SNPs were included in this score.

Medication Effects. Results of the analysis testing for association between brain volume measures and history of ADHD medication use are shown in Table S3. As a follow-up, we also performed a logistic regression analysis testing for association between the ADHD PGS and history of ADHD medication use. The ADHD PGS did not significantly predict medication history ($p = 0.34$), suggesting the effect of ADHD medication use on brain volume is independent of diagnosis. Table S4 shows the correlations among total brain volume, medication history, and parent-reported total scores on the ADHD Rating Scale.

Brain Volume Polygenic Scores. Linear regression was used to test for association between each polygenic score and the corresponding volume in the OHSU cohort, adjusting for age at scan, sex, motion and, for subcortical structures, whole brain volume.

Whole brain, putamen and thalamus volumes were significantly associated with their corresponding polygenic scores (Table S5). Our findings are consistent with estimates of the heritability of these brain volumes; specifically that intracranial volume, putamen and thalamus have the highest heritabilities (0.88, 0.89 and 0.88, respectively), while nucleus accumbens and amygdala have the lowest (0.49 and 0.43, respectively) (24).
We also tested differential associations with these PGS between the sexes. However, sex interaction terms were not significant for any of the brain volume measures. And because none of the genome-wide significant SNPs showed sex effects in the original ENIGMA GWAS, we felt confident in ruling-out sex effects for these polygenic scores. Sex interaction terms were dropped from the regression model and only main effects are reported in Table S5.

Table S1. Medications

ADHD Medications	**Disallowed Medications**
Adderall	Abilify
Adderall XR	Anafranil
Catapres	Ativan
Clonidine	Buspar
Concerta	Celexa
Cylert	Cymbalta
Daytrana Patch	Depakote
Desoxyn	Effexor
Dexedrine Capsules	Elavil/Endep
Dexedrine Tablets	Emsam Patch
DextroStat	Eskalith ER
Focalin Tablets	Geodon
Guanfacine/Intuniv	Guanfacine/Intuniv
Metadate CD Capsules	Haldol
Metadate ER Capsules	Klonopin
Methylin ER Tablets	Lamictil
Methylin Tablets	Lexapro
Provigil	Librium
Quillavant	Lithobid
Ritalin HCl	Luvox
Ritalin LA	Nardil
Strattera	Navane
Tenex	Norpramine
Vyvanse	Pamelor
	Parnate
	Paxil
	Prozac
	Remeron
	Risperdal
	Seroquel
	Serzone
	Tegretol

	Tofranil
	Topamax
	Trazadone
	Trileptal
	Valium
	Wellbutrin
	Xanax
	Zoloft
	Zyprexa

Table S2. Correlations among ADHD diagnosis, total brain volume and ADHD PRS

	ADHD Diagnosis	Total Brain Volume	ADHD PRS (p<0.5)	ADHD PRS (p<0.2)	ADHD PRS (p<0.1)	ADHD PRS (p<0.05)
ADHD Diagnosis	1.0	-0.069	0.12	0.12	0.14	0.13
Total Brain Volume		1.0	-0.084	-0.098	-0.085	-0.083
ADHD PRS (p<0.5)			1.0	0.96	0.91	0.84
ADHD PRS (p<0.2)				1.0	0.94	0.86
ADHD PRS (p<0.1)					1.0	0.92
ADHD PRS (p<0.05)						1.0

Table S3. Brain volumes associated with ADHD medication history.

Region	**Meds *d*‡**	**P (FDR)‡**	**Meds *d***	**P (FDR)**	**Sex * Meds P (FDR)**	**Meds *d*, males**	**P (FDR), males**	**Meds *d*, females**	**P (FDR), females**
Whole Brain	-0.372	0.0106 (0.0954)	-0.277	0.0565 (0.254)	0.675 (0.868)	-0.326	0.0615 (0.277)	-0.476	0.0829 (0.405)
Accumbens	0.180	0.214 (0.642)	0.215	0.139 (0.417)	0.420 (0.756)	0.258	0.139 (0.417)	-0.0235	0.932 (0.938)
Amygdala	0.0674	0.641 (0.921)	0.0696	0.632 (0.879)	0.869 (0.869)	0.0883	0.611 (0.843)	0.0539	0.844 (0.938)
Caudate	-0.0304	0.834 (0.938)	-0.00582	0.968 (0.968)	0.801 (0.869)	-0.0348	0.841 (0.864)	-0.0214	0.938 (0.938)
Cerebellum	-0.0526	0.716 (0.921)	-0.153	0.291 (0.655)	0.167 (0.752)	-0.124	0.477 (0.843)	0.306	0.266 (0.405)
Hippocampus	0.114	0.431 (0.799)	0.0121	0.933 (0.968)	0.285 (0.756)	-0.0296	0.864 (0.864)	0.370	0.180 (0.405)
Pallidum	-0.00497	0.973 (0.973)	-0.0758	0.602 (0.879)	0.362 (0.756)	-0.0922	0.595 (0.843)	0.304	0.270 (0.405)
Putamen	0.111	0.444 (0.799)	0.0590	0.684 (0.879)	0.662 (0.868)	0.0773	0.656 (0.843)	0.370	0.180 (0.405)
Thalamus	-0.250	0.0858 (0.386)	-0.379	0.00955 (0.0860)	0.0344 (0.310)	-0.442	0.0119 (0.107)	0.331	0.230 (0.405)

‡ Effect and p-value from model without the sex interaction term (main effect).

Table S4. Correlations among medication history, brain volume and ADHD symptom scores

	ADHD Med History	Total Brain Volume	Parent Total ADHD-RS
ADHD Med History	1.0	-0.143	0.600
Total Brain Volume		1.0	-0.113
Parent Total ADHD-RS			1.0

Table S5. Brain volumes associated with ENIGMA polygenic scores.

Region/PGS	PGS β	P (FDR)
Whole Brain*	**0.123**	**0.0158 (0.0423)**
Whole Brain**	**0.238**	**2.65e-6 (2.38e-5)**
Accumbens	0.0558	0.267 (0.305)
Amygdala	-0.00137	0.976 (0.976)
Caudate	0.0659	0.137 (0.183)
Hippocampus	0.0948	0.0294 (0.0588)
Pallidum	0.0714	0.114 (0.182)
Putamen	**0.126**	**0.00524 (0.0209)**
Thalamus	**0.109**	**0.00180 (0.0144)**

Each brain region was tested for association with its corresponding polygenic score (i.e. genetic factors associated with the volume of that particular brain region). *ICV-PGS based on ENIGMA data only. **ICV-PGS based on the combined ENIGMA+CHARGE consortium data.

Table S6. Hemisphere-specific brain volumes associated with ADHD status

Region	**ADHD *d*‡**	**P (FDR)‡**	**ADHD *d***	**P (FDR)**	**Sex * ADHD P (FDR)**
Accumbens (left)	0.0330	0.782 (0.865)	-0.0502	0.673 (0.718)	0.321 (0.715)
Accumbens (right)	-0.0137	0.909 (0.909)	0.0616	0.605 (0.698)	0.344 (0.715)
Amygdala (left)	-0.0297	0.802 (0.865)	0.0278	0.816 (0.816)	0.506 (0.735)
Amygdala (right)	0.0285	0.811 (0.865)	0.0606	0.611 (0.698)	0.612 (0.735)
Caudate (left)	0.310	0.0101 (0.0984)	0.303	0.0116 (0.112)	0.391 (0.715)
Caudate (right)	0.299	0.0123 (0.0984)	0.294	0.0140 (0.112)	0.402 (0.715)
Cerebellum (left)	-0.221	0.0640 (0.146)	-0.276	0.0214 (0.114)	0.169 (0.715)
Cerebellum (right)	-0.227	0.0570 (0.146)	-0.244	0.0418 (0.131)	0.369 (0.715)
Hippocampus (left)	-0.0518	0.664 (0.865)	-0.109	0.359 (0.574)	0.361 (0.715)
Hippocampus (right)	-0.0988	0.407 (0.636)	-0.0805	0.500 (0.667)	0.953 (0.953)
Pallidum (left)	-0.0926	0.437 (0.636)	-0.0827	0.488 (0.667)	0.880 (0.939)
Pallidum (right)	-0.0939	0.430 (0.636)	-0.124	0.298 (0.530)	0.496 (0.735)
Putamen (left)	-0.246	0.0398 (0.146)	-0.261	0.0293 (0.117)	0.347 (0.715)
Putamen (right)	-0.243	0.0419 (0.146)	-0.230	0.0544 (0.131)	0.572 (0.735)
Thalamus (left)	0.210	0.0814 (0.163)	0.227	0.0575 (0.131)	0.380 (0.715)
Thalamus (right)	0.237	0.0473 (0.146)	0.218	0.0687 (0.137)	0.643 (0.735)

‡ Effect and p-value from model without the sex interaction term (main effect).

Table S7. Hemisphere-specific brain volumes associated with PGC ADHD polygenic score.

Region	**PGS β‡**	**P (FDR)‡**	**PGS β**	**P (FDR)**	**Sex * PGS P (FDR)**
Accumbens (left)	0.0212	0.685 (0.783)	-0.0466	0.462 (0.778)	0.0621 (0.326)
Accumbens (right)	0.0999	0.0544 (0.651)	0.103	0.105 (0.778)	0.941 (0.941)
Amygdala (left)	0.0482	0.322 (0.769)	0.0426	0.474 (0.778)	0.869 (0.941)
Amygdala (right)	0.0777	0.0823 (0.651)	0.0523	0.336 (0.778)	0.416 (0.571)
Caudate (left)	-0.00151	0.974 (0.974)	0.0246	0.660 (0.841)	0.415 (0.571)
Caudate (right)	0.0221	0.625 (0.769)	0.0471	0.393 (0.778)	0.428 (0.571)
Cerebellum (left)	-0.0319	0.463 (0.769)	0.00668	0.899 (0.959)	0.203 (0.464)
Cerebellum (right)	-0.0245	0.578 (0.769)	0.0289	0.589 (0.841)	0.0815 (0.326)
Hippocampus (left)	0.0600	0.199 (0.769)	0.0990	0.0825 (0.778)	0.232 (0.464)
Hippocampus (right)	0.0342	0.450 (0.769)	0.0385	0.486 (0.778)	0.892 (0.941)
Pallidum (left)	0.0382	0.431 (0.769)	0.00117	0.984 (0.984)	0.274 (0.487)
Pallidum (right)	0.0728	0.122 (0.651)	0.0234	0.683 (0.841)	0.131 (0.419)
Putamen (left)	0.0230	0.619 (0.769)	-0.0730	0.190 (0.778)	**0.00273 (0.0307)**
Putamen (right)	0.0435	0.350 (0.769)	-0.0498	0.375 (0.778)	**0.00384 (0.0307)**
Thalamus (left)	-0.0200	0.591 (0.769)	-0.0515	0.255 (0.778)	0.223 (0.464)
Thalamus (right)	0.00323	0.929 (0.974)	-0.00964	0.828 (0.946)	0.611 (0.752)

‡ Effect and p-value from model without the sex interaction term (main effect).

* Effects in bold are statistically significant after FDR correction (α = 0.05) for the 16 volumes tested.

Figure S1. Enrollment flow chart.

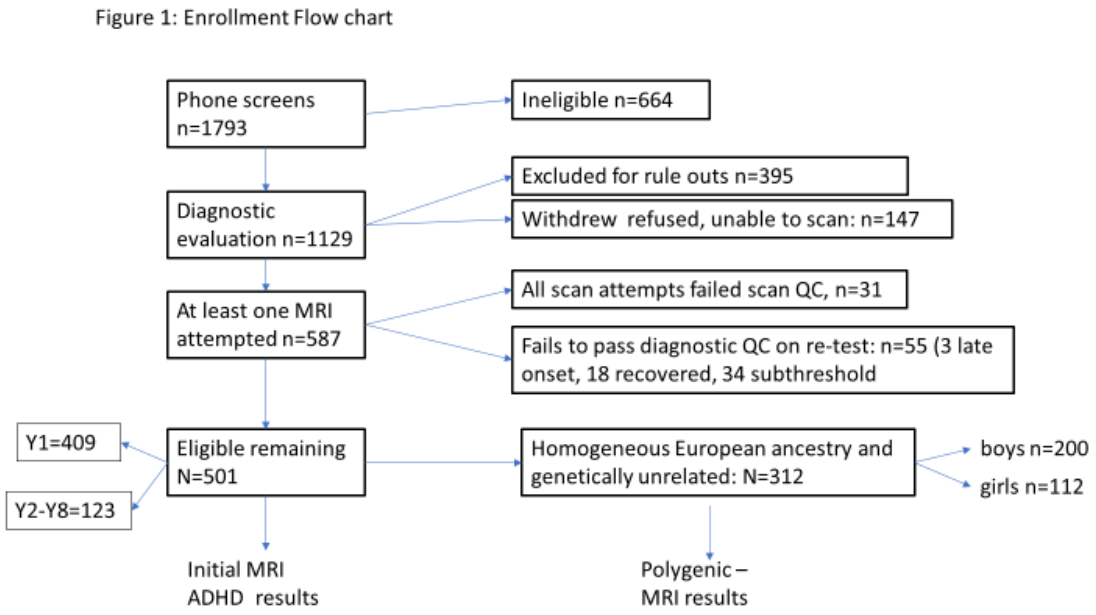


Figure S2. Whole brain and subcortical volumes stratified by sex and ADHD status. The volumes reported for each subcortical region are the averages of left and right volumes.

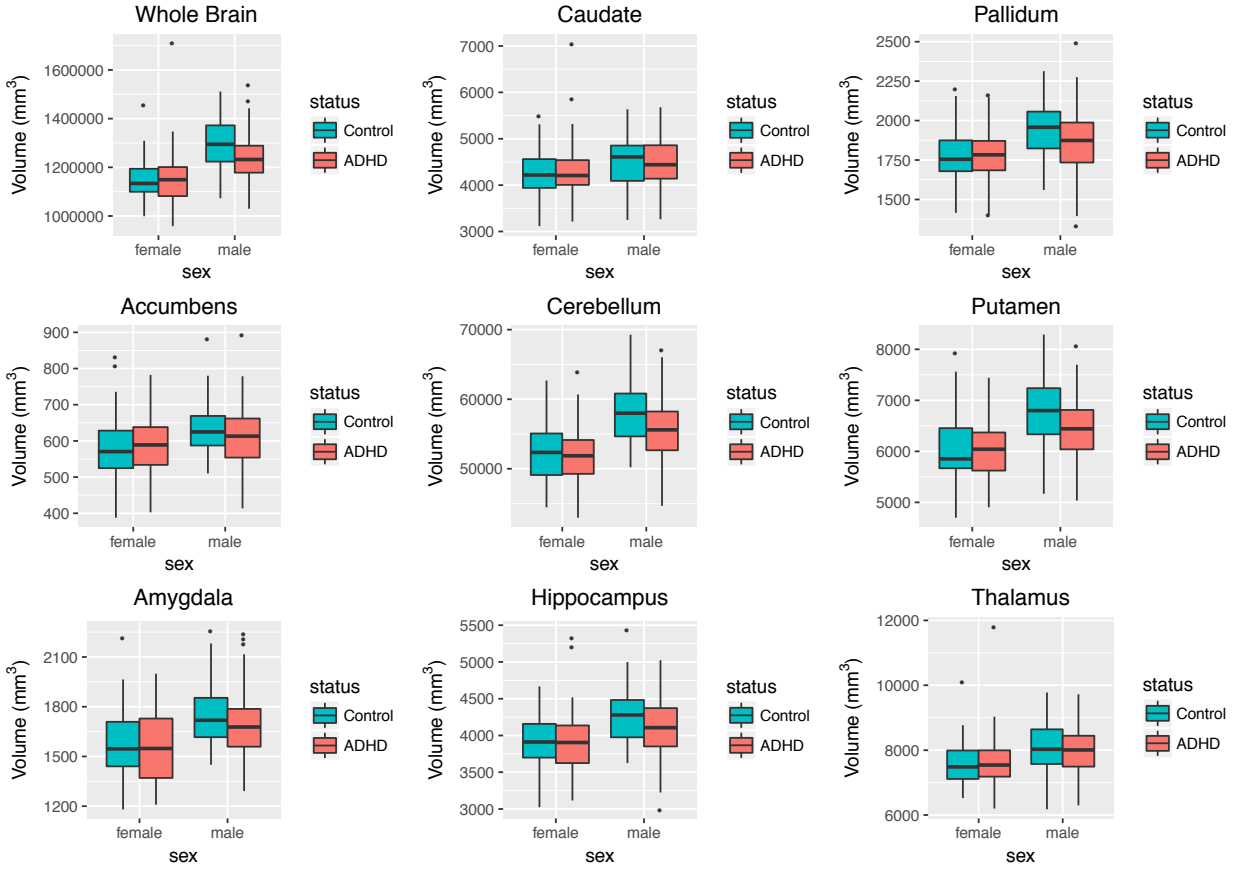
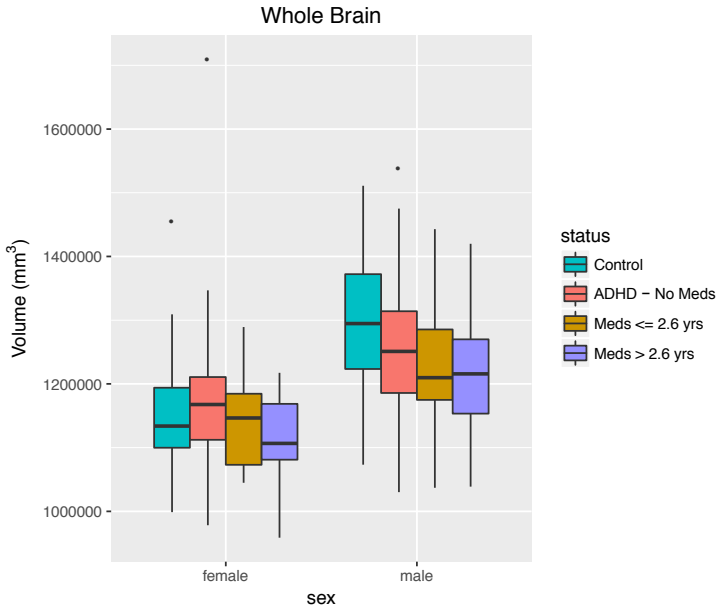


Figure S3. Medication Effects.



The distribution of whole brain volumes vs. ADHD status and medication use, stratified by sex. The median duration of medication use among ADHD patients = 2.6 years.

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