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CONTENTS

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eMethods 1. The ADHD-200 Cohort

The ADHD-200 is a multi-center study, and each site was approved by the local research ethics review boards. Signed informed consents were obtained from all participants or their legal guardians before participation. Inclusion criteria included: no history of neurological diseases and other chronic medical conditions; estimates of full-scale IQ above 80; psychostimulant drugs were withheld at least 24-48 hours before scanning. Data was downloaded from the ADHD-200 consortium website (http://fcon_1000.projects.nitrc.org/indi/adhd200).

In the present study, we used data from 4 sites (Peking University [PKU], NeuroIMAGE sample [NeuroIMAGE], New York University Child Study Center [NYU] and Oregon Health & Science University [OHSU]) which recruited both patients with ADHD and typically-developed controls (TD). In total, there were 233 patients and 267 controls. IQ was available in 3 sites (i.e. PKU, NYU and OHSU); the Wechsler Intelligence Scale for Chinese Children-Revised was used in PKU, and the Wechsler Abbreviated Scale of Intelligence was used in NYU and OHSU. The descriptive statistics of IQ was presented in Table S2. TD had significantly higher IQ than ADHD patients across 3 sites, while no difference between medicated and never-medicated samples. ADHD symptom measure was available in 3 sites (i.e. PKU, NYU and OHSU); ADHD Rating Scale IV was used in PKU, Conners' Parent Rating Scale-Revised, Long version was used in NYU, and Connors' Rating Scale-3rd Edition was used in OHSU. Detailed demographic characteristics between medicated and never-medicated patients was presented in Table S3. In the data collection site at NYU, we found medicated patients were older than never-medicated

subjects. We have already controlled for age in our analysis reported in the main text. Nonetheless, to confirm there was no important difference in our reported findings, we reanalyzed the data leaving the NYU site out. The main results remained significant. In the data collection site at OHSU, we found medicated patients were more likely to be a combined subtype, and also had more severe inattentive and hyperactive-impulsive symptoms. The main results remained significant when leaving the OHSU site out.

eMethods 2. Measurement of Delay Discounting

In the IMAGEN study, participants completed the computer-administered version of Monetary Choice Questionnaire (MCQ) (1), which is considered as the most extensively validated delay discounting task (2). It contains 27 dichotomous choice items pitting a smaller-immediate reward against a larger delayed reward for three levels of reward magnitude (i.e. small [€25–35], medium [€50–60], large [€75–85]), such as "Would you prefer €54 today or €55 in 117 days?" Answers were self-paced and made by clicking on one of two digital response buttons with a computer mouse.

The discounting rate was estimated by fitting to a hyperbolic function: $V = A/(1+kD)$, where V is the current subjective value of the delayed reward, A is the absolute value of the delayed reward, D is the length of delay in days, and k is a constant representing the magnitude of the

discounting function (3). Past researches have demonstrated that delay discounting is better described by hyperbola-like functions than by exponential decay functions (4, 5). Therefore, a fixed indifference k-value, which means the value of the discount rate at which the immediate and delayed rewards are of equal value, could be calculated for each 27 items. The individual discounting values were estimated as the geometric mean between the lowest implied indifference k-value in which subjects chose the delayed option, and the highest implied indifference k-value in which subjects chose the immediate option. In addition, as a measure of internal reliability, a consistency value was calculated for each subject as the proportion of responses that were consistent with that subject's k-value. We excluded the participants whose consistency scores were less than 75%, as recommended by the literature (6). A k-estimate was produced for each category of reward magnitude. Higher values of k represent greater preference for small immediate rewards and higher impulsivity. We used the geometric mean of the resulting small, medium, and large k-values, and normalized it by logarithmic transformation (6).

eMethods 3. MRI Data Preprocessing

High resolution T1-weighted magnetization prepared gradient echo sequence was collected using 3T scanners. All data were preprocessed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) using the VBM8 toolbox with default settings. Processing began by segmenting images into gray matter,

white matter and cerebrospinal fluid probability maps using a unified segmentation routine (7). Next, individual images were registered to the DARTEL template provided in VBM8. All images were subjected to nonlinear modulations and corrected for each individual head size. Gray matter images were then smoothed with an 8 mm full width at half maximum Gaussian kernel with the resulting voxel size $1.5mm^3$.

eMethods 4. Genotyping

DNA purification and genotyping were performed by the Centre National de Génotypage. DNA was extracted from whole-blood samples (~10 mL) preserved in BD Vacutainer EDTA Tubes (Becton, Dickinson and Company) using the Gentra Puregene Blood Kit (QIAGEN Inc.) according to the manufacturer's instructions. SNPs with call rates of <98%, minor allele frequency <1%, or deviation from the Hardy–Weinberg equilibrium ($p<1.00\times10^{-4}$) were excluded from the analyses. Individuals with an ambiguous sex code, excessive missing genotypes (failure rate>2%), and outlying heterozygosity (heterozygosity rate of 3 SDs from the mean) were also excluded.

eResults 1. Associations of Other ADHD Assessments With the Brain Clusters

We found small to medium associations between parent- and youth-rated ADHD symptoms (r=0.24-0.44), and a small correlation between youth-rated symptoms and ADHD polygenic risk score (r=0.08). ADHD symptoms measured by either youth SDQ or parent DAWBA were significantly associated with the brain clusters identified by parent SDQ (prefrontal cluster: r=-0.08 and -0.09, $p<0.001$; posterior-occipital cluster: r=-0.1 and -0.06, $p<0.008$).

eResults 2. Supplementary Results With IQ as a Covariate

After controlling for full-scale IQ, the associations of ADHD total score with both clusters remained significant (the prefrontal cluster: r=-0.09, 95% CI=-0.13, -0.04; the posterior-occipital cluster: r=-0.08, 95% CI=-0.12, -0.03; 95% CI was given by 5,000 bootstraps). Similar results were found if controlling for verbal IQ only.

eResults 3. Comparison of Participants With Persistent ADHD Symptoms With Well-Matched Controls

To balance the sample sizes in group comparisons, we used the "MatchIt" R package to define a well-matched control group based on sex, handedness, site and TIV (8). For the same ANCOVAs as in the main text, we found similar significant results but with stronger effect sizes (prefrontal cluster: 5.63 mL±1.03 vs. 6.27 mL±1.32, $F_{1,75}$=6.33, p=0.014, η_p^2= 0.078; posterior-occipital cluster: 2.06 mL±0.35 vs. 2.23 mL±0.24, $F_{1,75}$=6.57, p=0.012, η_p^2= 0.081).

TABLE S1. Characteristics of the study population in the ADHD-200 cohort

	ADHD patients (n=233)	TD controls (n=267)
Male	188 (80.7%)	141 (52.8%)
Age (year)	11.75±3.01	11.98±3.04
Subtypes of ADHD diagnosis		
Combined subtype	129 (55.4%)	-
Hyperactive/impulsive subtype	8 (3.4%)	-
Inattentive subtype	96 (41.2%)	-
Medication status (78 missing)		
Medicated	56 (36.1%)	-
Never-medicated	99 (63.9%)	-
Site		
Peking University	78 (33.5%)	116 (43.4%)
NeuroIMAGE sample	20 (8.6%)	23 (8.6%)
New York University Child Study Center	101 (43.3%)	90 (23.7%)
Oregon Health & Science University	34 (14.6%)	38 (14.2%)

TABLE S2. Descriptive statistics of IQ within sites in the ADHD-200 cohort

	PKU		NYU		OHSU	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
Medicated ADHD patients	108.15 (14.37)	26	102.14 (12.60)	21	105.25 (14.54)	8
Never-medicated ADHD patients	104.02 (12.45)	52	106.89 (13.14)	27	109.05 (13.99)	19
Typically-developed controls	118.18 (13.35)	115	111.02 (14.22)	83	118.87 (13.02)	38
F statistics	22.48		3.8		5.42	
p	<0.001		0.025		0.007	
Post-hoc comparison (LSD correction)	TD>med=nomed		TD>med		TD>nomed=med	

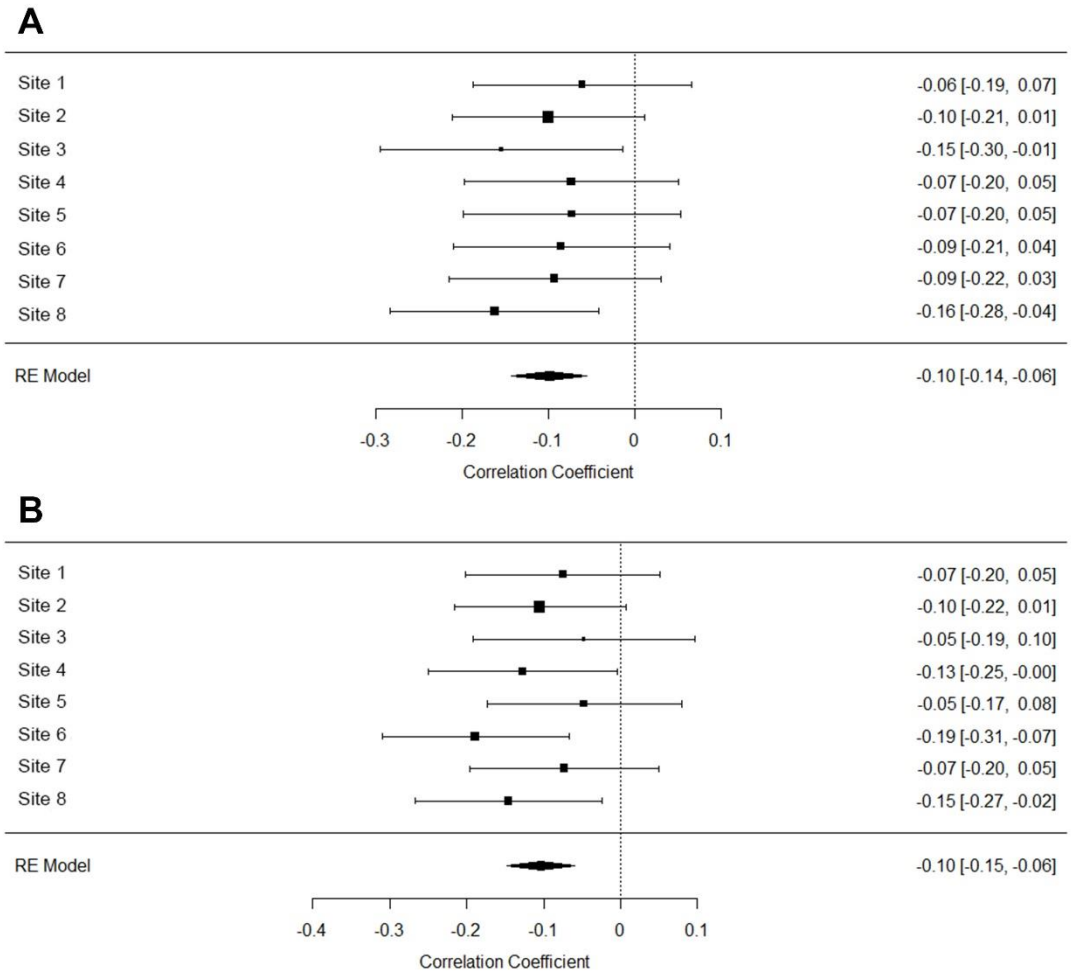
PKU=Peking University, NYU=New York University Child Study Center, OHSU=Oregon Health & Science University.

TABLE S3. Descriptive statistics of demographic characteristics between medicated and never-medicated patients in the ADHD-200 cohort

	PKU			NYU			OHSU		
	Medicated	Never-med	p	Medicated	Never-med	p	Medicated	Never-med	p
Age	11.79 (2.07)	12.67 (1.89)	0.07	13.78 (2.84)	10.22 (2.44)	**<0.001**	9.38 (1.76)	8.8 (0.71)	0.4
Sex			0.26			0.26			0.94
Female	1 (3.8%)	6 (11.5%)		4 (18.2%)	9 (32.1%)		2 (25%)	5 (26.3%)	
Male	25 (96.2%)	46 (88.5%)		18 (81.8%)	19 (67.9%)		6 (75%)	14 (73.7%)	
Handedness			0.61			0.21			
Right	25 (96.2%)	51 (98.1%)		19 (86.4%)	20 (71.4%)		8 (100%)	19 (100%)	
Left	1 (3.8%)	1 (1.9%)		3 (13.6%)	8 (28.6%)		0	0	
FSIQ	108.15 (14.37)	104.02 (12.45)	0.19	102.14 (12.6)	106.89 (13.14)	0.21	105.25 (14.54)	109.05 (13.99)	0.53
Diagnosis			0.1			0.64			0.09
Combined	13 (50%)	16 (30.8%)		14 (63.6%)	16 (57.1%)		7 (87.5%)	8 (42.1%)	
H-I	0	0		0	0		0	1 (5.3%)	
IN	13 (50%)	36 (69.2%)		8 (36.4%)	12 (42.9%)		1 (12.5%)	10 (52.6%)	
ADHD measure									
H-I	23.83 (7.46)	22.23 (6.03)	0.33	67 (12.42)	68.11 (12.64)	0.77	80.5 (10.39)	64.74 (12.07)	**0.004**
IN	29 (3.67)	27.89 (3.61)	0.23	67.65 (7.90)	72.21 (9.20)	0.08	78.5 (6.61)	70.11 (6.25)	**0.004**

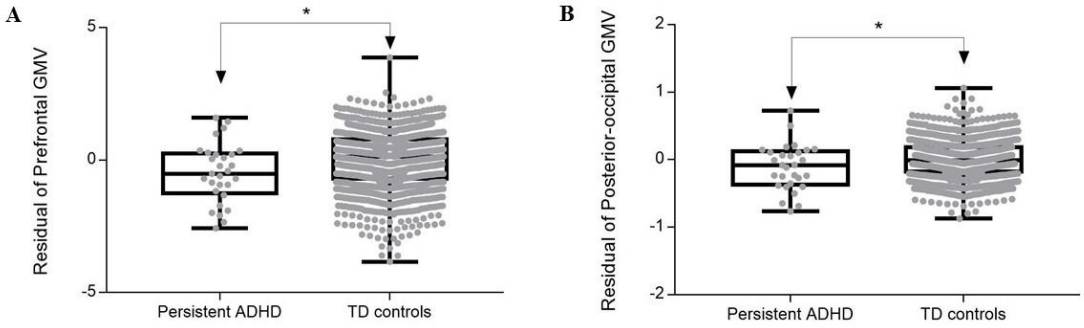
PKU=Peking University, NYU=New York University Child Study Center, OHSU=Oregon Health & Science University.

FIGURE S1. Forest plots of meta-analysis across 8 data collection sites in the IMAGEN cohort



Results were estimated by random-effects model. A. Associations between GMV of the prefrontal cluster and ADHD total score. B. Associations between GMV of the posterior-occipital cluster and ADHD total score.

FIGURE S2. Box-and-whisker plot showing differences of GMVs in two ROIs between adolescents with persistent ADHD (N=29) and typically-developed controls (N=1,278) in the IMAGEN cohort



A. Difference of GMV of the prefrontal cluster. B. Difference of GMV of the posterior-occipital cluster. Y axis was the residual of the GMV regressed on age, sex, handedness, TIV and site. Bottom and top of the box are the minimum and maximum, and the band near the middle of the box is the median. *, $p<0.05$.

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