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Supplementary information

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Cortical thinning and hippocampal expansion as brain signatures of attention deficit hyperactivity disorder symptom trajectories

In the format provided by the authors and unedited

Supplementary Materials

Contents

eMethod 1. Sample selection

Population-based cohort

ABCD study

This study selected 7,436 adolescents (3,850 males [51.78%]) for analysis from the Adolescent Brain and Cognitive Development (ABCD) study, which included 11,877 adolescents from 21 sites (https://nda.nih.gov/abcd). (**Fig S1**). Our exclusion criteria are as follows: 1) adolescents were not assessed or data missing for the Child Behavior Checklist-ADHD symptoms at the baseline, 1-year follow-up (FU1), and 2-year follow-up (FU2) ($n = 3{,}979$); 2) trajectories of adolescent ADHD symptoms did not meet the literature's definitions of persistent, remitting, emergent, and control groups[1] ($n = 462$); 3) structural MRI data missing or did not pass MRI quality control at baseline ($n = 315$)[2]; 4) structural MRI data missing or did not pass MRI quality control at FU2 ($n = 1{,}327$)[2]. Finally, 7,436 adolescents were included in the behavioral data analysis, 7,121 adolescents at baseline, and 6,109 adolescents at FU2 were included in the neuroimaging data analysis.

IMAGEN cohort

This study selected 109 adolescents (58 males [53.21%]) for analysis from the IMAGEN cohort, which included 2,000 adolescents from 8 sites[3] (**Fig S2**). Our exclusion criteria are as follows: 1) adolescents were not assessed or data missing for the Strengths and Difficulties Questionnaire-Hyperactivity/inattention symptoms at the wave1 (age 14), wave2 (age 16), and wave 3 (age 19) ($n = 792$); 2) trajectories of

adolescent ADHD symptoms did not meet the literature's definitions of persistent, remitting, and emergent groups[1] ($n = 1086$); 3) structural MRI data missing and MRI quality control at both wave1 and wave3($n = 13$)[3]. Finally, 109 adolescents were included in the analysis to validate the brain signatures of ADHD symptom trajectories.

Clinical-based cohort

ADHD-1000

The Oregon ADHD-1000 is a case-control study approved by the institutional review board[4]. Our inclusion criteria are as follows: 1) no history of neurological disorders and other chronic medical conditions (e.g., autism spectrum disorder or intellectual disability); 2) the full-scale IQ score above 75; 3) passed quality-controlled data. After quality control, a total of 742 patients with ADHD (519 males [69.95%], 9.64 ± 1.80 years old) were included in the present study to validate the neural correlates of ADHD and the medication effects on multiple functions, such as sleep (**Table S1**). Details on the operating procedure have been published elsewhere[4].

ADHD-200

The ADHD-200 is a multi-center study approved by the research ethics review board at eight sites. Our inclusion criteria are as follows: 1) no history of neurological disorders and other chronic medical conditions; 2) the estimated full-IQ score above 75; 3) passed visual check of structural MRI data. After quality control, a total of 263 patients with ADHD (201 males [76.4%]; 10.89 ± 2.44 years old) from five sites (*i.e.*,

Peking University, Kennedy Krieger Institute, New York University Child Study Center, Oregon Health & Science University, and University of Pittsburgh) were included in the present study to validate the neural correlates of ADHD (**Table S2**).

ADHD-Shanghai

The ADHD-Shanghai is a longitudinal clinical dataset (from November 2015 to August 2024), approved by the research ethics review board at the Fudan University. Our inclusion criteria are as follows: 1) no history of neuropsychiatric disorders and comorbidities, including depression, autism, conduct disorder, epilepsy, etc.; 2) the estimated full-IQ score above 75; 3) multiple time-point ADHD diagnoses (≥ 2) with consistent dates of Swanson, Nolan, and Pelham rating scale (SNAP, Chinese version)[5] measurements and diagnosis; 4) age, sex, and medication information for ADHD were complete. After quality control, a total of 1,868 patients with ADHD (4,932 clinical visits) were included in the present study to validate the effect of ADHD medication on ADHD symptoms at follow-up (**Table S3**). ADHD diagnosis was completed by experienced clinical psychologist (Supplementary Method 2).

eMethod 2. Assessments of behavioural phenotypes

ADHD symptoms

ABCD study

Child Behavior Checklist (CBCL)[6]. ADHD symptoms were assessed using the parents/guardians-reported DSM-oriented ADHD scale of CBCL. Higher scores

indicate severer ADHD symptoms.

Brief Problem Monitor (BPM)[7]. To address the issue of different informants, we also used the ASEBA Brief Problem Monitor (BPM)[7] to assess the inattention symptoms at baseline, FU1, and FU2 by different informant, i.e., the adolescents' teachers at school. We further validated the brain signatures of the remitting group using the teacher-rated inattention t-score and linear regression. The covariates included age and sex, parental education and family income, race, the site variable, and delta ICV.

Internalizing symptoms. The internalizing symptoms were assessed using the parents/guardians-reported CBCL internalizing scale, which provides an overall measure of internalizing problems (*i.e*., anxious/depressed, withdrawn/depressed, and somatic complaints) [6]. Higher scores indicate severer internalizing problems.

IMAGEN cohort

Strengths and Difficulties Questionnaire (SDQ)[8]. ADHD symptoms, conduct problems, peer relationship problems, and emotional symptoms were assessed using the youth-reported SDQ at all waves. Higher Hyperactivity/inattention scores indicate severer ADHD symptoms.

ADHD-1000

In the ADHD-1000 clinical study, ADHD symptoms was assessed by parent-rated the

Conners Rating Scales-3rd Edition short form (Conners-III)[9], Strengths and Difficulties Questionnaire long form including the impairment module[10], the ADHD Rating Scale for DSM (ADHD-RS)[11], and a semi-structured clinical interview administered by a trained Master's-degree level clinician (Kiddie Schedule for Affective Disorders and Schizophrenia)[12]. ADHD diagnosis was performed by a best estimate DSM diagnosis was established by a diagnostic team clinicians[4]. Blind to one another's ratings, they formed a diagnostic opinion based on all available information. Given the completeness of the ADHD symptom assessment information, the present study used the ADHD-RS to measure symptoms in patients with ADHD. Higher scores indicate severer ADHD symptoms.

ADHD-200

In the ADHD-200 clinical study, ADHD symptoms was assessed by ADHD Rating Scale IV (ADHD-RS)[11], Conners' Parent Rating Scale-Revised, Long version (CPRS-LV)[13], and Connors' Rating Scale-3rd Edition[9]. ADHD diagnosis was independently completed by two experienced clinical psychologist. Higher scores indicate severer ADHD symptoms.

ADHD-Shanghai

In the ADHD-Shanghai clinical study, ADHD symptoms was assessed by the Swanson, Nolan, and Pelham rating scale (SNAP, Chinese version)[5]. ADHD diagnosis was completed by experienced clinical psychologist. Higher scores indicate severer ADHD

symptoms.

Sleep problems

ADHD-1000

In the ADHD-1000 clinical sample, sleep problems was assessed using the Children Sleep Habit Questionnaire, which has been demonstrated to be a promising assessment tool for sleep quality ($\text{Cronbach's alpha} = 0.78$) in children[14]. In the ADHD-1000 dataset, we tested whether medicated ADHD patients exhibited more sleep problems compared to non-medicated ADHD patients.

Emotion dysregulation

ADHD-1000

In the ADHD-1000 clinical sample, emotion dysregulation was assessed using the Temperament in Middle Childhood Questionnaire, which has been demonstrated to be a promising assessment tool for emotion regulation ($\text{Cronbach's alpha} = 0.74$) in children[15]. In the ADHD-1000 dataset, we tested whether medicated ADHD patients exhibited more emotional dysregulation compared to non-medicated ADHD patients.

We used linear regression analyses to examine whether medicated ADHD patients exhibited more sleep and emotional problems compared to non-medicated ADHD patients in the ADHD-1000 cohort.

eMethod 3. MRI data preprocessing

ABCD study

In the ABCD study, structural neuroimaging measures were evaluated on 3T MRI scanners across the 21 sites (https://abcdstudy.org/)[16]. Adolescents completed MRI scans of high-resolution (1-mm isotropic, protective motion correction) 3D T1-weighted images. Cortical surface reconstruction was processed by FreeSurfer, version 5.3[17], using a standardized ABCD pipeline, which mainly included registration, intensity normalization and bias field correction[16]. Structural data that did not pass quality-control procedures performed in the ABCD Study were excluded. In the present study, we focused on cortical thickness and surface area, and subcortical volume corresponding to the Desikan-Killiany[18] ($n = 68$) and aseg[19] ($n = 14$) atlas, respectively.

IMAGEN cohort

In the IMAGEN cohort, structural MRI data were collected on 3T MRI scanners at eight sites. Imaging protocols were harmonised across sites and scanners. Additionally, based on the ADNI protocol, high-resolution 3D T1-weighted images (1.1 mm isotropic) were acquired with a gradient-echo sequence (http://adni.loni.usc.edu/methods/mri-analysis/mri-acquisition). Cortical surface reconstruction was processed by FreeSurfer[17], and the preprocessing pipeline mainly included registration, intensity normalization and bias field correction[16]. Structural data that did not pass quality-control procedures performed in the IMAGEN cohort were excluded.

ADHD-1000

In the ADHD-1000 clinical sample, the preprocessing procedures and quality control of neuroimaging data was conducted based on the HCP-ABCD pipiline[4], complemented by our own visual inspection of structural images. Only T1-weighted images that passed quality control were processed using recon-all as implemented in FreeSurfer[17].

ADHD-200

In the ADHD-200 clinical sample, the preprocessing procedures of neuroimaging data was conducted based on the literature[20], and quality assessments (questionable vs. pass) was complemented by visual inspection. T1-weighted images that passed quality control were processed using recon-all as implemented in FreeSurfer[17].

eMethod 4. Genotyping data and polygenetic analysis

Genotyping data. Genotyping was obtained from whole blood or saliva samples of ABCD participants, including 11,099 unique individuals with 516,598 genetic variants (*i.e.*, single-nucleotide polymorphisms (SNPs)). In addition, we downloaded summary statistics from the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/download-results/adhd/) for the most well-powered ADHD genome-wide association study (GWAS) with 20,183 ADHD patients and 35,191 control subjects as the discovery dataset[21].

Quality control. After quality control and data matching, this study included 6,302 samples and 350,622 SNPs were available for calculating the polygenic risk score (PRS) for ADHD. Quality control specifically included the exclusion of SNPs with minor allele frequencies (MAF) < 1% or imputation information scores (INFO) < 0.8, and SNPs with call rates < 0.95 and MAF < 1%. Individuals with high missing rates (>5%) and autosomal heterozygosity deviations not within ± 3 SD were also excluded. SNPs were further filtered for call rates ≥ 0.98 and Hardy-Weinberg p values > 10^{-6}. Sex checks were performed to eliminate mismatches between biological sex and reported sex in subsequent analyses[22]. Dosage data were converted to hard-call genotypes using the genetic analysis tool Plink (version 1.90, https://www.cog-genomics.org/plink2/), and only SNPs with an imputation r^2 score ≥ 0.3 were transferred to PRS[23].

Polygenic analysis. The ABCD samples contain siblings and diverse ethnicity, which might bias the statistical results due to the relatedness and population stratification[24,25]. Therefore, we used Plink to calculate PRS under P-value thresholds at 0.001, 0.05, 0.10, 0.20, 0.30, 0.40, 0.50[26] in the ABCD European samples. The primary analysis is based on the threshold of $p < 0.05$, because it maximally captures phenotypic variance in GWAS[27,28]. As an exploratory, supplementary analysis, we also used other thresholds for PRSs ranging from $p < 0.5$ to 0.001, as well as the PRS_mean. After randomly selecting one participant from each family, we tested the between-group differences between the distinct trajectories of ADHD symptoms using ANCOVA, where covariates included age, sex, parental education and family income, the site variable,

and the first 10 principal components (PCs)[29,30].

eMethod 5. The predictive model

In the ABCD study, we built the predictive model using SVR (5-fold cross-validation with 200 random repetitions) to test its specificity in predicting ADHD symptoms at 3-year follow-up among all individuals who experienced high-ADHD symptoms. The predictive features included the age and sex, parental education and family income, and six brain signatures identified in the main text (*i.e.*, CLBM model). The dependent variables, psychiatric symptoms, including ADHD, anxiety, conduct, depressive, opposition, and somatic symptoms, were assessed using the CBCL parent/guardian-reported scales at FU3[6]. Higher scores indicate more severe symptoms. We assessed the model performances by the correlation between (*i.e.,* R^2) predicted and real symptoms (paired t-test, $p < 0.05$).

In the IMAGEN cohort, we built the SVR model (5-fold cross-validation with 200 random repetitions) to validate the superiority and specificity of these brain signatures in predicting ADHD symptoms at age 23 (wave4) using both behavioral and neuroimaging data ($n = 109$). To validate the superiority, we built the 'clinical + longitudinal brain' model (CLBM) using nine features including age and sex, the baseline ADHD symptom scores, and the brain signatures identified in the ABCD study. The 'clinical + baseline brain' model (CBBM) also used nine features including age and sex, the baseline ADHD symptom scores, and the baseline values of these brain

signatures. To validate the specificity, the predictive model included age and sex, and six brain signatures identified in the ABCD study (*i.e.*, CLBM model). The dependent variables, psychiatric symptoms, including inattention/hyperactivity, conduct, peer, and emotion symptoms were assessed using the SDQ youth-reported scales at age 23 (wave4)[8] (Supplementary Method 2). Higher scores indicate more severe symptoms. We assessed the model performances by the correlation between (*i.e.,* R^2) predicted and real symptoms (paired t-test, $p < 0.05$).

All predictive models were implemented using the Python (version 3.11.3) package 'scikit-learn' (version 1.3.0).

eMethod 6. Correlation analysis of hippocampal volumetric expansion and PRS for ADHD

Since the volume of the left hippocampus was expanding in all four trajectory subgroups ADHD symptoms in the ABCD study, and the trend of the level of the PRS for ADHD was persistent > emergent > remitting > control, we randomly sampled one participant from each family of the European samples in the ABCD study and used linear regression to investigate the association between hippocampal expansion and the PRS for ADHD. Here, the PRS for ADHD was calculated using GWAS SNPs with $p <$ 0.05 (eMethod 4). The covariates included age and sex, parental education and family income, the site variable, environmental factors, delta intracranial volume (ICV), and the first 10 principal components (PCs)[29,30].

eMethod 7. Mediation analysis

After randomly sampled one participant from each family, we performed the mediation analysis to test the mediation effect of the changes of ADHD symptoms on the association between hippocampal expansion and the changes of school performance among individuals who experienced high-ADHD symptom ($n = 323$). The covariates included age and sex, parental education and family income, race, the site variable, and delta ICV. The mediation analysis was conducted using the R (version 4.3.0) package bruceR with 5,000 bootstraps (version 2023.8.23).

eMethod 8. Validation of the effects of ADHD medication on the follow-up ADHD symptoms in the ADHD-Shanghai dataset

In the ADHD-Shanghai clinical sample, we recorded the prescribed dosages of commonly used ADHD medications, including Methylphenidate, Ritalin, Concerta, Atomoxetine, and Clonidine. We then used the visit-by-dosage interaction term in a linear mixed-effects model (lmerTest package, version 3.1-3) to estimate the association between cumulative ADHD medication dosage over three or more years and ADHD symptoms. The children's age, gender, and family income were included as covariates with subject_ID modeled as the random effect.

eMethod 9. Growth mixture model

We conducted the growth mixture model (GMM)[31] in Mplus version 8[32] to identify the

latent trajectories of ADHD symptoms (i.e., ADHD t score) across BL, FU1 and FU2 among individuals who experienced high-ADHD symptoms ($n = 381$).

eResult 1. Hippocampal volumetric expansion was associated with the PRS for ADHD

Linear regression analysis showed a significant association between the left hippocampal volumetric expansion and the PRS for ADHD ($\beta = -8.40, 95\%\ \mathrm{CI} = [-16.96, -0.15];\ P = 0.045;\ \eta_p^2 = 1.67 \times 10^{-3}$).

eResult 2. Mediation result

Mediation analysis indicated that the changes of ADHD symptoms had a significant mediating effect on the association between the left hippocampal volumetric expansion and changes of school performance among individuals who experienced high-ADHD symptom (Indirect effect: $\beta = 0.025, 95\%\ \mathrm{CI} = [0.001, 0.068];\ P = 0.047$ given by 5,000 bootstraps).

eResult 3. Meta-analytic results on the brain signatures of ADHD symptom trajectories

After randomly selected one participant from each family 10 times, we used the ANCOVA to test the group differences in the brain signatures of ADHD symptom trajectories identified in the main text (two-sided). Next, we conducted a random-effect meta-analysis to validate the robustness of these brain signatures.

Persistent vs control:

the right caudal middle frontal gyrus (cMGF.R) (mean difference (MD) $= -0.008, 95\%\ \mathrm{CI} = [-0.010, -0.006];\ P < 0.001$)

the left superior frontal gyri (SFG.L): ($\mathrm{MD} = -0.005, 95\%\ \mathrm{CI} =$

$[-0.007, -0.004]$; $P < 0.001$)

the right superior frontal gyri (SFG.R): ($\mathrm{MD} = -0.005, 95\%\ \mathrm{CI} = [-0.007, -0.004]$; $P < 0.001$)

Emergent vs control:

the right posterior cingulate (PCC.R): ($\mathrm{MD} = 0.008, 95\%\ \mathrm{CI} = [0.005, 0.010]$; $P < 0.001$)

the right insula (INS.R): ($\mathrm{MD} = 0.021, 95\%\ \mathrm{CI} = [0.017, 0.025]$; $P < 0.001$)

cMGF.R: ($\mathrm{MD} = 0.010, 95\%\ \mathrm{CI} = [0.007, 0.013]$; $P < 0.001$)

Remitting vs control:

the left hippocampus (Hipp.L): ($\mathrm{MD} = 0.012, 95\%\ \mathrm{CI} = [0.009, 0.014]$; $P < 0.001$)

Remitting vs persistent:

Hipp.L: ($\mathrm{MD} = 0.014, 95\%\ \mathrm{CI} = [0.010, 0.018]$; $P < 0.001$)

SFG.R: ($\mathrm{MD} = 0.006, 95\%\ \mathrm{CI} = [0.004, 0.008]$; $P < 0.001$)

cMFG.R: ($\mathrm{MD} = 0.013, 95\%\ \mathrm{CI} = [0.010, 0.016]$; $P < 0.001$)

Emergent vs persistent:

cMFG.R: ($\mathrm{MD} = 0.017, 95\%\ \mathrm{CI} = [0.014, 0.021]$; $P < 0.001$)

SFG.L: ($\mathrm{MD} = 0.007, 95\%\ \mathrm{CI} = [0.005, 0.010]$; $P < 0.001$)

SFG.R: ($\mathrm{MD} = 0.007, 95\%\ \mathrm{CI} = [0.004, 0.009]$; $P < 0.001$)

Emergent vs remitting:

Hipp.L ($\mathrm{MD} = -0.017, 95\%\ \mathrm{CI} = [-0.022, -0.012]$; $P < 0.001$)

PCC.R ($\mathrm{MD} = 0.009, 95\%\ \mathrm{CI} = [0.007, 0.013]$; $P < 0.001$)

INS.R ($\mathrm{MD} = 0.018, 95\%\ \mathrm{CI} = [0.013, 0.023]$; $P < 0.001$)

eResult 4. Meta-analytic results of the faster hippocampal volumetric expansion

associated with reduced inattention symptoms in the remitting group

After randomly selected one participant from each family 10 times, we used the linear regression to test the association between the increased left hippocampal volume and reduced inattention symptoms in the remitting group (two-sided), and conducted a random-effect meta-analysis to validate the robustness of the association ($\beta = -0.057, 95\%\ \mathrm{CI} = [-0.086, -0.023];\ P < 0.001$).

eResult 5. Meta-analytic results of the slower cortical thinning in the posterior cingulate cortex associated with increased inattention symptoms in the emergent group

After randomly selected one participant from each family 10 times, we used the linear regression to test the association between the reduced right posterior cingulate thickness and increased inattention symptoms in the emergent group (two-sided), and conducted a random-effect meta-analysis to validate the robustness of the association ($\beta = 0.498, 95\%\ \mathrm{CI} = [0.176, 0.814];\ P < 0.001$).

eResult 6. The effect of a three-year period ADHD medication on sleep trajectories in the remitting group

In the ABCD cohort, we used linear mixed-effects model to examine the differences in the trajectory of sleep problems from baseline to the 3-year follow-up among individuals in the remitting group who continued ADHD medication from baseline to FU2 ($n = 11$), compared to those in the remitting group who did not take ADHD

medication during this period ($n = 92$). The model included the following covariates: age, sex, race, and parental education and income. The random effects were modeled with the subject nested within the site of data collection (two-sided).

The effects of a three-year period ADHD medication on the trajectory of sleep problems from baseline to the 3-year follow-up (FU3) (Fig. S4)

Visit: $\beta = -2.48, t = -7.09, P = 1.02 \times 10^{-11}$

*Visit*group:* $\beta = 2.36, t = 2.29, P = 0.023$

Additionally, in the remitting group, we tested the association between three-year cumulative dosage of stimulant drugs and non-stimulant drugs with sleep problems at FU3, with covariates including age, sex, race, and parental education and income, and the site variable (two-sided).

Non-stimulant: $\beta = 0.19, t = 2.25, P = 0.031, \eta_p^2 = 0.09$

eResult 7. The effects of ADHD medication on follow-up ADHD symptoms, sleep and emotional problems

As an exploratory analysis, among all individuals who experienced high-ADHD symptoms in the ABCD study, we performed linear regression to test whether individuals who took ADHD medication from baseline to FU2 exhibited more ADHD symptoms, sleep problems, and emotion dysregulation at both FU2 and FU3 compared to those who did not take ADHD medication from baseline to FU2. The findings were presented in Supplementary Tables 7-8.

Table S1. Demographic characteristics of ADHD-1000 participants (N=742)

Characteristics	ADHD patients (n = 742)
Basic Information	
Age (years)	9.64±1.80
Sex (Male, %)	519 (69.95%)
ADHD symptoms	
Total score	70.30±11.98
Inattention	71.11±11.71
Hyperactivity-impulsivity	66.46±13.52

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (percentage).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder.

Table S2. Demographic characteristics of ADHD-200 participants (N=263)

Characteristics	ADHD patients (n = 263)
Basic Information	
Age (years)	10.89±2.44
Sex (Male, %)	201 (76.43%)
ADHD symptoms	
Total score	64.41±13.39
Inattention	58.46±21.67
Hyperactivity-impulsivity	55.11±24.13
Site	
Peaking University	80 (30.4%)
Kennedy Krieger Institute	22 (8.4%)
New York University Child Study Center	118 (44.9%)
Oregon Health & Science University	39 (14.8%)
University of Pittsburgh	4 (1.5%)

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (percentage).

Table S3. Demographic characteristics of ADHD-Shanghai participants (N=1,868)

Characteristics	ADHD patients (n=1,868)
Basic Information	
Enrollment age: (years)	8.81±1.96
Sex (Male, %)	1,383 (74.04%)
Number (n/visit)	
Within two years	1,868/2,731

Over three or more years	658/2,201

Note: Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (percentage).

Table S4. No significant association between medication status and baseline ADHD symptoms and sleep problems in the remitting group

ADHD symptoms	β	t	*p*-value	η_p^2
Total	0.19	0.75	0.45	5.66e-03
Inattention	0.32	1.83	0.06	0.03
Hyperactivity	-0.13	-0.54	0.59	1.26e-03
Sleep problem	1.51	0.75	0.25	4.16e-03

Notes: The linear regression model was used to test the association between medication status and ADHD symptoms and sleep problems at baseline in the remitting group (two-sided).

Table S5. Individuals in the remitting group who had taken ADHD medications from baseline to FU2 had more ADHD symptoms and sleep problems at FU2

Phenotype	β	t	*p*-value	η_p^2
Total	0.90	2.58	0.011	0.05
Inattention	0.53	2.19	0.031	0.03
Hyperactivity	0.37	1.72	0.088	0.03
Sleep problem	5.84	3.91	1.54e-4	0.10

Notes: The linear regression model was used to test the relationship between medication status and ADHD symptoms as well as sleep problems at FU2 in the remitting group (two-sided). The findings correspond to the “ADHD medication effect” section of the in the statistical analysis of the main text.

Abbreviations: FU2, 2-year follow-up.

Table S6. Individuals in the remitting group who had taken ADHD medications from baseline to FU2 had more ADHD symptoms, sleep problems and emotion dysregulation at FU3

Phenotype	β	t	*p*-value	η_p^2
Total	1.53	3.00	0.003	0.08
Inattention	0.85	2.95	0.004	0.08
Hyperactivity	0.64	2.00	0.047	0.04

Sleep problem	5.70	3.36	0.001	0.09
Emotion dysregulation	6.39	3.44	0.0008	0.09

Notes: The linear regression model was used to test the relationship between medication status and ADHD symptoms as well as sleep problems at FU3 in the remitting group (two-sided).

Abbreviations: FU3, 3-year follow-up.

Table S7. Among all individuals who experienced high-ADHD symptom who had taken ADHD medications from baseline to FU2 had more ADHD symptoms and sleep problems at FU2

Phenotype	β	t	*p*-value	η_p^2
Total	1.46	4.09	5.28e-5	0.08
Inattention	0.54	3.09	0.002	0.05
Hyperactivity	0.92	3.92	0.0001	0.08
Sleep problem	3.04	2.28	0.022	0.02

Notes: The linear regression model was used to test the relationship between medication status and ADHD symptoms as well as sleep problems at FU2 among all individuals who experienced high-ADHD symptom (two-sided).

Abbreviations: FU2, 2-year follow-up.

Table S8. Among all individuals who experienced high-ADHD symptom who had taken ADHD medications from baseline to FU2 had more ADHD symptoms, sleep problems and emotion dysregulation at FU3

Phenotype	β	t	*p*-value	η_p^2
Total	1.14	3.09	0.002	0.07
Inattention	0.44	2.36	0.018	0.04
Hyperactivity	0.70	2.94	0.004	0.07
Sleep problem	0.84	1.99	0.047	0.01
Emotion dysregulation	5.32	2.26	0.019	0.03

Notes: The linear regression model was used to test the relationship between medication status and ADHD symptoms as well as sleep problems at FU3 among all individuals who experienced high-ADHD symptom (two-sided).

Abbreviations: FU2, 2-year follow-up; FU3, 3-year follow-up.

Table S9. Associations between faster hippocampal volumetric expansion and decreased ADHD symptoms

Condition	β	0.95CI	*p*-value	η_p^2
Remitting				
Total	-0.036	-7.94e-02, 7.47e-03	0.103	0.03
Inattention	-0.056	-0.111, -0.002	0.041	0.04
Hyperactivity	-0.109	-0.336, 0.116	0.336	4.91e-03
Remitting - additionally controlling for medication status				
Total	-0.034	-7.72e-02, 9.15e-03	0.121	0.03
Inattention	-0.056	-0.110, -0.001	0.046	0.04
Hyperactivity	-0.100	-0.322, 0.123	0.374	5.16e-03
Remitting - additionally controlling for the baseline ADHD symptoms				
Total	-0.033	-7.64e-02, 1.02e-02	0.132	0.03
Inattention	-0.057	-0.112, -0.003	0.039	0.04
Hyperactivity	-0.093	-0.318, 0.132	0.411	5.08e-03
Remitting - additionally controlling for the PRS of ADHD				
Total	-0.138	-0.272, -0.003	0.045	8.18e-03
Inattention	-0.176	-0.344, -0.008	0.041	0.02
Hyperactivity	-0.110	-0.349, 0.128	0.350	4.55e-03
Among all individuals who experienced high-ADHD symptoms				
Total	-0.105	-0.233, 0.023	0.107	0.02
Inattention	-0.139	-0.259, -0.019	0.023	0.03
Hyperactivity	-0.083	-0.210, 0.044	0.197	1.00e-02
Among all individuals who experienced high-ADHD symptoms – PSM				
Total	-2.606	-4.927, -0.285	0.027	0.01
Inattention	-1.315	-2.572, -0.059	0.040	0.02
Hyperactivity	-2.115	-4.560, 0.340	0.091	0.01
Remitting- BPM				
Inattention	-0.446	-0.820, -0.072	0.028	0.18

Notes: The linear regression model and weighted propensity score matching (PSM) were used to test the association/potential causal effect between the hippocampal growth and decreased ADHD symptoms (two-sided).

Abbreviations: BPM, the ASEBA Brief Problem Monitor; CI, confidence interval.

Table S10. Associations between slower cortical thinning in the posterior cingulate cortex and increased ADHD symptoms

Condition	β	0.95CI	*p*-value	η_p^2
Emergent				
Total	0.193	-0.692, 0.215	0.291	0.02
Inattention	0.492	0.047, 0.931	0.031	0.03
Hyperactivity	0.012	-0.342, 0.366	0.944	5.19e-03
Emergent- additionally controlling for medication status				
Total	0.157	-0.714, 0.200	0.259	0.02
Inattention	0.512	0.070, 0.953	0.025	0.03
Hyperactivity	0.026	-0.331, 0.383	0.883	5.32e-03
Emergent - additionally controlling for the baseline ADHD symptoms				
Total	0.076	-0.343, 0.190	0.160	0.06
Inattention	0.400	0.012, 0.788	0.044	0.05
Hyperactivity	0.105	-0.223, 0.433	0.518	6.76e-03
Emergent - additionally controlling for the PRS of ADHD				
Total	-0.332	-0.782, 0.117	0.138	4.00e-02
Inattention	0.707	0.227, 1.187	0.006	0.12
Hyperactivity	-0.058	-0.415, 0.298	0.734	8.74e-03
Among all individuals who experienced high-ADHD symptoms				
Total	0.066	-0.062, 0.194	0.309	2.85e-03
Inattention	0.131	0.007, 0.255	0.039	0.01
Hyperactivity	0.092	-0.034, 0.218	0.150	7.14e-03
Among all individuals who experienced high-ADHD symptoms – PSM				
Total	2.285	-2.458, 7.028	0.344	1.86e-04
Inattention	2.163	-0.125, 4.452	0.064	5.02e-03
Hyperactivity	3.463	-0.976, 7.903	0.126	4.49e-03

Notes: The linear regression model and weighted propensity score matching (PSM) were used to test the association/potential causal effect between the reduced posterior cingulate thickness and increased ADHD symptoms (two-sided).

Abbreviations: CI, confidence interval.

Table S11. The superiority of the CLBM model in predicting ADHD symptoms at

FU3 in the ABCD study

	Prediction performance (R^2)			t/ p-value
Prediction Model (SVR)	The clinical model	The 'clinical + baseline brain' model (CBBM)	The 'clinical + longitudinal brain' model (CLBM)	CLBM v.s. CBBM
Total	0.088	0.089	0.114	7.594/4.692e-14
Inattention	0.031	0.042	0.050	3.415/0.0006
Hyperactivity	0.143	0.172	0.203	8.452/5.489e-17

Notes: We built three predictive models using SVR (5-fold cross-validation with 200 random repetitions) to test the superiority of the CLBM model in predicting ADHD symptoms at FU3. Next, we used the paired t-test to examine the prediction performance of these predictive models (two-sided).

Abbreviations: FU3, 3-year follow-up.

Table S12. The specificity of the CLBM model in predicting ADHD symptoms at FU3 in the ABCD study

	Prediction performance (R^2)	t/p-value
Prediction Model (SVR)	The 'clinical + longitudinal brain' model (CLBM)	
ADHD	0.071	
Depression	0.009	40.97/2.72e-225
Anxiety	0.010	40.24/6.66e-221
Conduct	0.026	26.24/4.03e-127
Opposite	0.020	31.48/1.14e-165
Somatic	0.025	26.59/7.21e-130

Notes: We built the predictive model using SVR (5-fold cross-validation with 200 random repetitions) to test the specificity of the CLBM model in predicting ADHD symptoms at FU3. Next, we used the paired t-test to examine the prediction performance (two-sided) (eMethod 5).

Abbreviations: FU3, 3-year follow-up.

Table S13. Validating the specificity of the CLBM model in predicting ADHD symptoms at wave4 in the IMAGEN cohort

Prediction performance (R^2)

Prediction Model (SVR)	The 'clinical + longitudinal brain' model (CLBM)	t/*p*-value
ADHD	0.037	
Conduct	0.024	6.92/6.33e-12
Peer	0.030	3.55/3.93e-4
Emotion	0.042	-1.91/0.056

Notes: We built the predictive model using SVR (5-fold cross-validation with 200 random repetitions) to test the specificity of the CLBM model in predicting ADHD symptoms at wave4 (age 23) in the IMAGEN cohort. Next, we used the paired t-test to examine the prediction performance (two-sided) (eMethod 5).

Table S14. Validating the association between faster hippocampal volumetric expansion and decreased ADHD symptoms in the IMAGEN cohort

Condition	β	0.95CI	*p*-value	η_p^2
Remitting				
Hyperactivity/inattention	-1.61	-3.082, -0.133	0.033	0.02
Remitting - additionally controlling for the baseline ADHD symptoms				
Hyperactivity/inattention	-1.59	-3.051, -0.127	0.034	0.02
Remitting – PSM				
Hyperactivity/inattention	-1.51	-2.920, -0.003	0.035	0.03
Remitting – PSM and additionally controlling for the baseline ADHD symptoms				
Hyperactivity/inattention	-1.22	-2.427, -0.004	0.049	0.03

Notes: The linear regression model and propensity score matching (PSM) were used to test the association/potential causal effect between the hippocampal growth and decreased ADHD symptoms in the IMAGEN cohort (two-sided).

Abbreviations: CI, confidence interval.

Table S15. Associations between the volume of hippocampus and inattention symptoms in two ADHD clinical samples

Condition	β	0.95CI	*p*-value	η_p^2
ADHD-1000				
Inattention	-2.79	-4.77, -0.83	0.006	0.04
ADHD-1000 - additionally controlling for medication status				

Inattention	-2.64	-4.53, -0.76	0.006	0.05
ADHD-1000 – patients without taking ADHD medication				
Inattention	-2.65	-4.92, -0.37	0.028	0.01
ADHD-200 - standardized β				
Inattention	-0.07	-0.12, -0.01	0.020	0.34
ADHD-200 - additionally controlling for medication status (standardized β)				
Inattention	-0.07	-0.13, -0.02	0.007	0.25
ADHD-200 - patients without taking ADHD medication (standardized β)				
Inattention	-0.09	-0.15, -0.02	0.009	0.03

Abbreviations: CI, confidence interval.

Table S16. Associations between ADHD medication and ADHD symptoms in ADHD-Shanghai dataset

Condition	β	0.95CI	*p*-value	η_p^2
Over three or more years				
Total	0.039	0.016, 0.061	6.38e-04	8.51e-03
Inattention	0.018	0.008, 0.027	3.12e-04	9.28e-03
Hyperactivity	0.015	0.006, 0.023	5.56e-04	8.84e-03

Note: We used the visit-by-dosage interaction term in a linear mixed-effects model to estimate the association between cumulative ADHD medication dosage over three or more years and ADHD symptoms (two-sided).

Abbreviations: CI, confidence interval.

Table S17. ADHD medication information at baseline, FU1 and FU2 for each ADHD symptom trajectory subgroup.

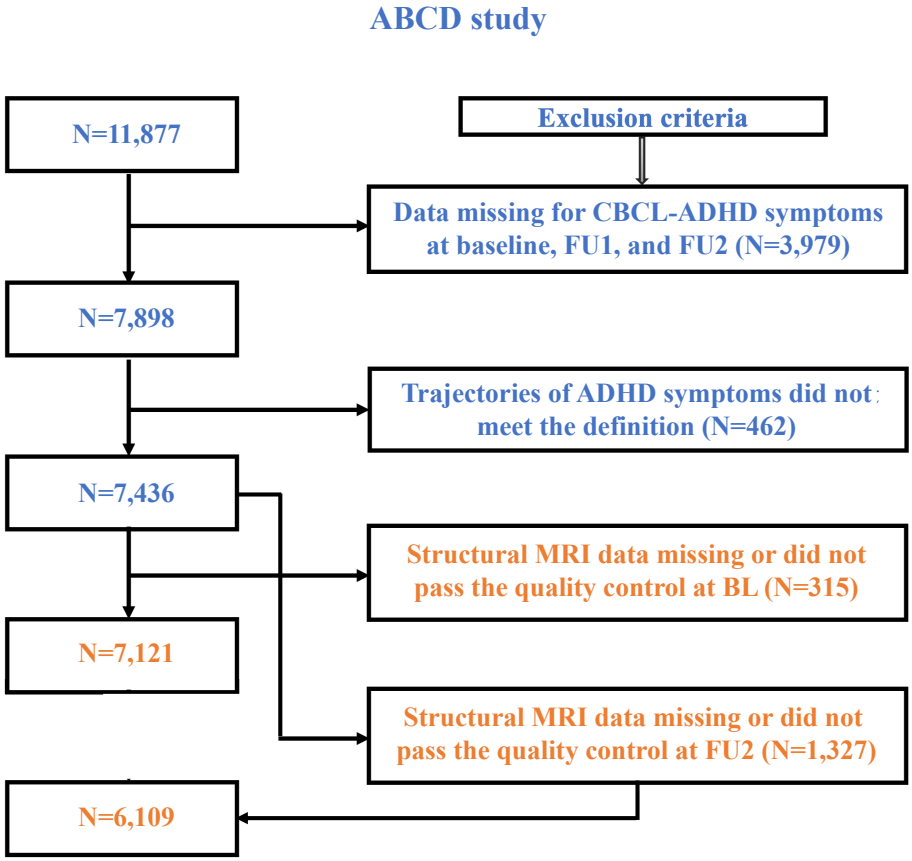
Persistent (n = 164)	Baseline	1-year follow-up	2-year follow-up
methylphenidate	44	31	32
amphetamine	31	26	26
Non-stimulant medication	35	27	28
Remitting (n = 141)	Baseline	1-year follow-up	2-year follow-up
methylphenidate	18	18	17

amphetamine	13	12	8
Non-stimulant medication	13	13	8
Emergent (n = 76)	Baseline	1-year follow-up	2-year follow-up
methylphenidate	13	10	9
amphetamine	5	6	10
Non-stimulant medication	5	5	6

Notes: Each data represents: number of medicated individuals.

Abbreviations: FU1, 1-year follow-up; FU2, 2-year follow-up.

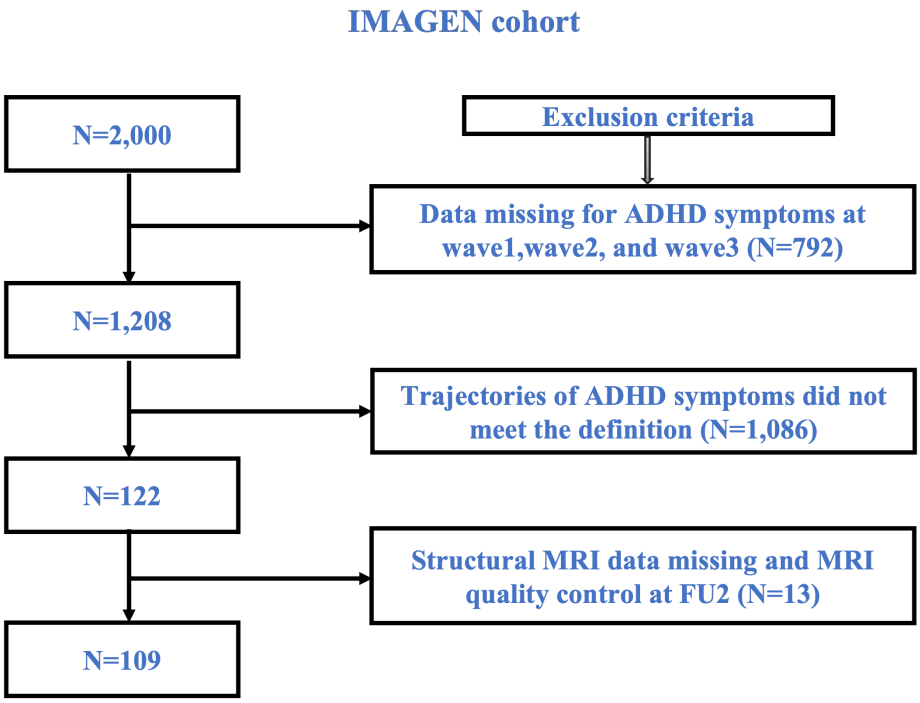
Fig S1. Flowchart for selecting subjects from the ABCD study



Notes: For behavioral data analysis, 7,436 subjects were included in this study (marked in blue). For neuroimaging analysis, 7,121 adolescents at baseline and 6,109 adolescents at FU2 were included in this study (marked in yellow).

Abbreviations: ABCD, Adolescent Brain and Cognitive Development; ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist; BL, baseline; FU1, 1-year follow-up; FU2, 2-year follow-up.

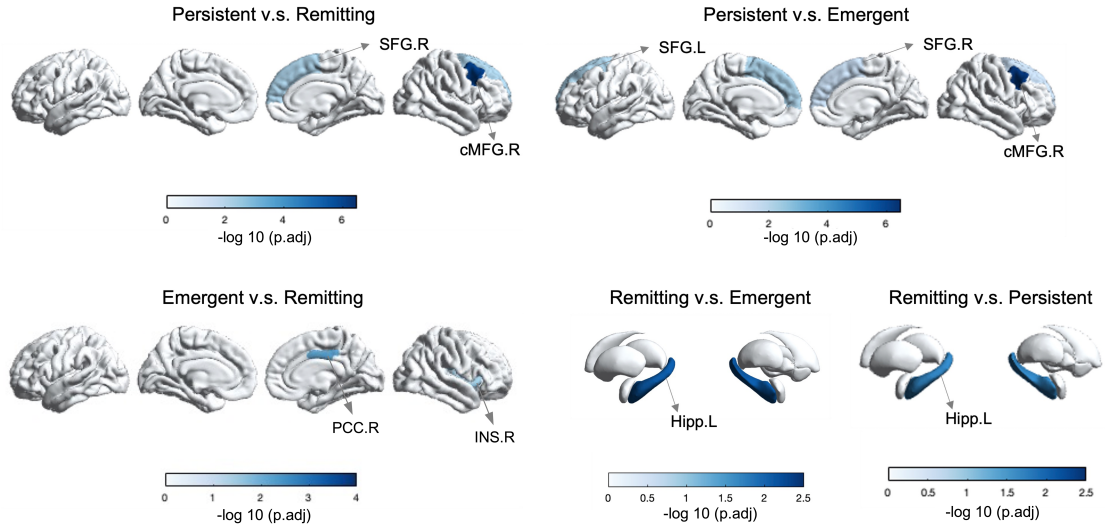
Fig S2. Flowchart for selecting subjects from the IMAGEN cohort



Notes: For validation analysis, 109 subjects were included in the IMAGEN cohort.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder.

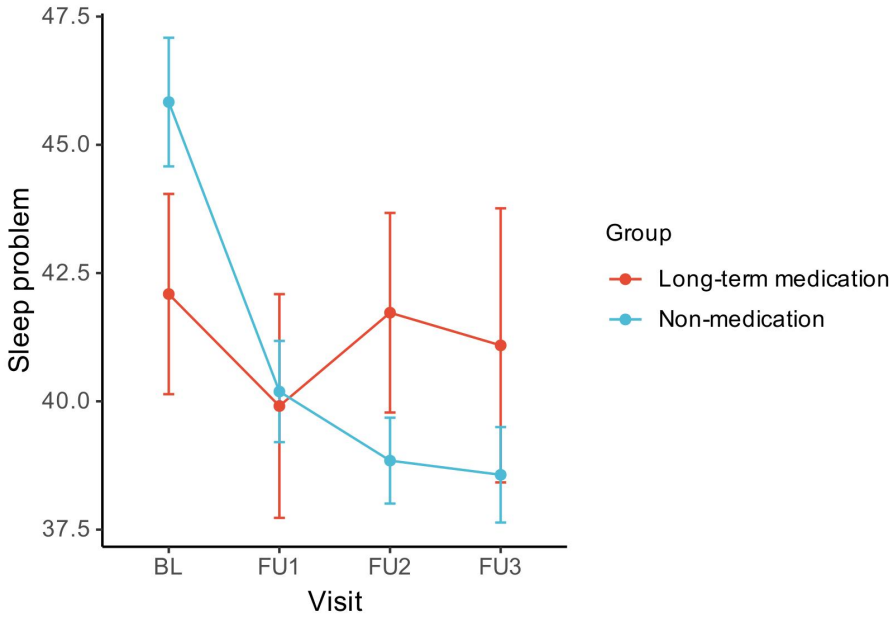
Fig S3. Brain signatures of ADHD symptom trajectory subgroups



Notes: The ANCOVA analysis was used to test the difference in brain signatures among ADHD symptom subgroups (two-sided). The FDR correction was applied, followed by followed by Tukey's honestly significant difference (HSD) test for post hoc pairwise comparisons. The brain maps were generated based on the main analysis findings.

Abbreviations: cMFG, caudal middle frontal gyrus; SFG, superior frontal gyri; INS, insula, PCC, posterior cingulate cortex; Hipp, hippocampus; L, left; R, right.

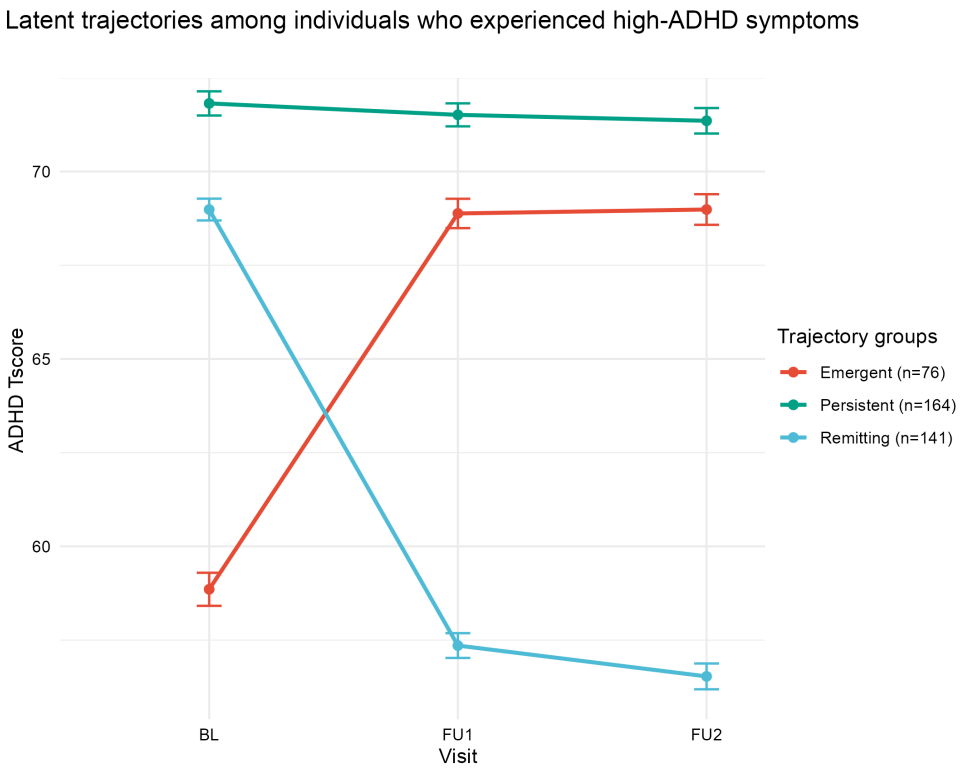
Fig S4. The effects of a three-year period ADHD medication on the trajectory of sleep problems in the remitting group



Notes: The linear mixed-effects model was used to test the differences in the trajectory of sleep problems from baseline to the FU3 among individuals in the remitting group who continued ADHD medication for three years from baseline to FU2 (i.e., Long-term medication, $n = 11$), compared to those in the remitting group who did not take ADHD medication (i.e., Non-medication, $n = 92$) (two-sided). The error bar indicates the standard error of the mean value.

Abbreviations: BL, baseline; FU1, 1-year follow-up; FU2, 2-year follow-up; FU3, 3-year follow-up.

Fig S5. The latent trajectories among individuals who experienced high-ADHD symptoms



Notes: The growth mixture model was applied to identify the latent trajectories of ADHD symptoms across BL, FU1 and FU2 among individuals who experienced high-ADHD symptoms. The error bar denotes standard error of mean value. The error bar indicates the standard error of the mean value.

Abbreviations: BL, baseline; FU1, 1-year follow-up; FU2, 2-year follow-up.

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