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이학석사 학위논문

Dissecting the heterogeneity of the brain structure in attention-deficit/hyperactivity disorder and its clinical associations

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Dissecting the heterogeneity of the brain structure in attention-deficit/hyperactivity disorder and its clinical associations

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is one of childhood's most common neurodevelopmental disorders, typically characterized by inattention, impulsivity, and hyperactivity. Despite previous studies exploring brain abnormalities in ADHD, these studies have frequently compared ADHD to a control group, potentially overlooking the heterogeneity within ADHD. Given the challenge posed by the varying symptoms of ADHD in making accurate diagnoses and providing effective treatments, it is essential to understand the heterogeneity in ADHD. To this end, this study uncovered the heterogeneity of the structural brain in ADHD using unsupervised clustering modeling. The clustering model revealed two distinct groups of ADHD. Then, this study investigated the relationship between the identified ADHD subgroups and clinical characteristics in prepubertal children (ages 9-10 years old; the Adolescent Brain Cognitive Development study). Both subgroups showed higher levels of ADHD symptoms compared to non-ADHD individuals, but ADHD-2 had higher internalizing mood and genome-polygenic scores (GPSs) for bipolar disorder, BMI, and risk tolerance. The brain profiles of each subgroup showed that ADHD-1 had reduced cortical measures with only a few regions, while ADHD-2 had overall brain volume reductions and decreased surface area. Additionally, the longitudinal analysis revealed different developmental patterns, with ADHD-1 showing reductions in cortical and subcortical volume and ADHD-2 showing reduced cortical thickness. The findings suggest the possibility of different brain pathologies within ADHD and the need for further understanding to inform diagnostic strategies. In conclusion, this study sheds light on the heterogeneity of ADHD and the underlying brain differences between subgroups, providing insights for improved diagnostic and therapeutic approaches in the future.

Keyword: Attention-deficit/hyperactivity disorder; heterogeneity; neurosubtyping; unsupervised-clustering model

Student Number: 2020-20846

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1. INTRODUCTION

1.1. Background

1.1.1. Attention-deficit/hyperactivity disorder (ADHD)

1.1.1.1. ADHD in childhood

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood, typically characterized by inattention, impulsivity, and hyperactivity. To be diagnosed with ADHD, the symptoms must be present prior to the age of 12 and be observed across more than two different settings (American Psychiatric Association & Association, 2013). ADHD symptoms tend to lessen with age, but remain until adulthood (Faraone et al., 2015). For example, longitudinal studies of children with ADHD have revealed that at least 15% of them still continue to meet the full diagnostic criteria for ADHD at the age of 25, while 50% showed partial remission with persisting residual symptoms (Faraone et al., 2006). Researchers suggest that this age-dependent decrease in the prevalence of ADHD may be attributed to the late development of brain structures and functions associated with ADHD (Hoogman et al., 2017). Specifically, the delayed brain maturation and plasticity theory posits that the development of the ADHD brain is supported by the synaptic reinforcements that result from experiences, and that its maturation process is merely postponed (Casey et al., 2013; Whitford et al., 2007). However, despite life experience, many patients with ADHD do not reach the full developmental recovery as that of the controls. In addition, earlier onset age is a risk factor for the development of other comorbid psychiatric disorders, such as disruptive behavior disorders, anxiety and mood disorders, and other neurodevelopmental disorders (e.g., autism spectrum disorders (ASD) and learning disorders (LD)) (Nigg et al., 2020). Therefore, studying ADHD in childhood and implementing early interventions can greatly improve the future prospects of children with ADHD.

1.1.1.2. Structural brain abnormalities in ADHD

Preadolescent childhood is a critical developmental period that is accompanied by a series of changes in brain development. During this stage, preadolescents experience an increase in gray matter volume and surface area (Giedd et al., 1999; Wierenga et al., 2014). In particular, the gray matter in the frontal and parietal regions reaches its peak during early adolescence (Ball et al., 2019). These changes have a long-lasting impact on various aspects, such as cognitive function and mental health. However, ADHD is linked with structural abnormalities in the brain (Faraone et al., 2015), including the dorsolateral prefrontal (Shaw et al., 2014) and parietal cortex (Shaw et al., 2012) (**Figure 1**).

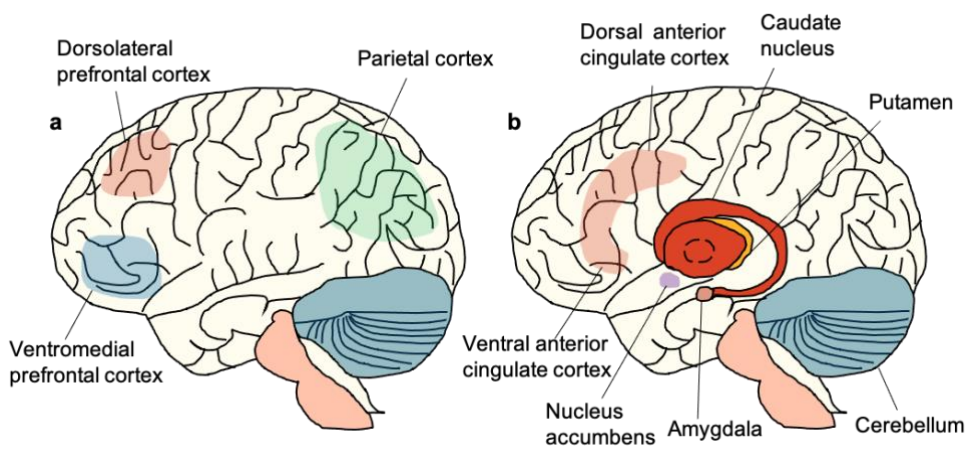

Figure 1. Brain abnormalities in ADHD. a, Cortical regions associated with ADHD. The dorsolateral prefrontal cortex is associated with working memory, the ventromedial prefrontal cortex with complex decision-making and strategic planning, and the parietal cortex with the orientation of attention. **b**, Subcortical regions associated with ADHD. The subcortical structures of the brain, such as the ventral and dorsal anterior cingulate cortex, basal ganglia (including nucleus accumbens, caudate nucleus, and putamen), the amygdala, and the cerebellum, have been found to have structural and functional abnormalities in individuals with ADHD.

In terms of brain morphometric abnormalities, a number of studies demonstrated that patients with ADHD show smaller total brain volume, which might be attributed to the reduction of gray matter (Castellanos et al., 2002; Durston et al., 2004; Greven et al., 2015). Volume reduction in the right globus pallidus, right putamen, caudate nucleus, and cerebellum has been consistently reported in ADHD patients (Frodl & Skokauskas, 2012; Stoodley & Schmahmann, 2009). For example, a recent cross-sectional mega-analysis study with data from the ENIGMA-ADHD Working Group reported that ADHD patients presented with reduced brain volume in estimated total intracranial volume (ETIV) and other subcortical regions, such as nucleus accumbens, amygdala, caudate, hippocampus, and putamen across the lifespan (age range 4-63 years) (Hoogman et al., 2017). Another study by the ENIGMA-ADHD group, using cortical measures, showed that ADHD children have differences in cortical surface area, while these differences are not found in adolescents and adults with ADHD (Hoogman et al., 2019). These findings suggest that the differences between ADHD and controls are more prominent and extensive in younger children than in older children and adolescents, necessitating further exploration into the ADHD brain in childhood. To this end, a recent study investigated structural brain abnormalities among children in the general population with the Adolescent Brain and Cognitive Development (ABCD) study (age range 9-10 years) (Bernanke et al., 2022). In line with previous structural findings of ADHD, Bernanke et al. (2022) demonstrated that ADHD children have significant reductions in brain measures, but mainly cortical surface area measures. Interestingly, this study with ABCD samples did not discover differences in the subcortical volumes (Bernanke et al., 2022), which many previous studies have found. Therefore, it is still necessary to further investigate these findings.

In addition to findings in morphometrical measurements, studies using diffusion-weighted imaging have reported alterations in the white matter microstructure of individuals with ADHD: frontostriatal tracts (Chiang et al., 2015;

Chiang et al., 2016), corpus callosum (Pastura et al., 2016; Wu et al., 2017), superior longitudinal fasciculus (decreased fractional anisotropy (FA) (Wu et al., 2017), increased mean diffusivity (MD) (Pastura et al., 2016)), cingulum (decreased FA (Tung et al., 2021), increased MD (Pavuluri et al., 2009)), thalamic radiations (decreased FA) (Bouziane et al., 2018), internal capsule (decreased FA) (Bouziane et al., 2018), and corona radiata (decreased FA) (Nagel et al., 2011). However, the direction of these abnormalities has been inconsistent, with some studies showing decreased and others increasing values in the same region. For example, while one study found decreased superior longitudinal fasciculus in ADHD (Chiang et al., 2016), another reported increased values (Connaughton et al., 2022; Silk et al., 2009). To clarify these conflicting findings and gain a better understanding, further investigation into the brain pathophysiology of ADHD is essential.

1.1.1.3. Genetic influences on ADHD

ADHD is largely explained by genetic risk factors. ADHD's heritability estimation is up to 76% (Wang et al., 2017), which indicates a great amount of inherited genetic effects. Other twin studies also show similar levels of heritability for ADHD of 70~80% both in children and adults (Asherson & Gurling, 2011; Faraone & Larsson, 2019; Faraone et al., 2005; Franke et al., 2012; Larsson et al., 2014). Large-scale genome-wide association studies (GWAS) have discovered common genetic variants contributing to ADHD (Demontis et al., 2019). Given that, a genome-wide polygenic score (GPS) could provide an estimation of the genetic influence on certain traits at the individual level (Choi et al., 2020). For example, a previous study demonstrated that ADHD GPS predicts ADHD traits and symptoms (i.e., pragmatic language ability and social cognition) (Martin et al., 2014). A recent study also demonstrated that the genetic risk of ADHD increased, as more stringent diagnostic criteria for ADHD were implemented (Cordova et al., 2022). However, it is noteworthy that the genetic variants linked to ADHD are also

related to other mental health traits, not just ADHD symptoms. For instance, a recent genome-wide meta-analysis study tested the genetic correlation of ADHD with 219 phenotypes using linkage disequilibrium (LD) score regression and revealed that ADHD genetically overlapped other phenotypes, including major depressive disorder (MDD), anorexia nervosa, educational outcomes, obesity-related phenotypes, neuroticism, cross disorder, body mass index (BMI), and insomnia (Demontis et al., 2019).

1.1.2. Heterogeneity in ADHD

An important issue regarding ADHD is that it is highly heterogeneous and can be attributed to a multifactorial inheritance (Posner et al., 2020). As a result of the ADHD heterogeneity, individuals with ADHD show diverse cognitive and behavioral profiles, comorbid disorders, and various long-term developmental trajectories (Schulz et al., 2017). The heterogeneity leads to the predicament in accurate diagnoses, followed by the prescription of ineffective treatments (Buch & Liston, 2021; Hong et al., 2020; Loo et al., 2018; Luo et al., 2019). Thus, it is essential to investigate the heterogeneity. However, the conventional approaches, which typically compare patients with controls by averaging the individual variability within the group, have limitations in exploring heterogeneity. That is, the traditional approaches tend to oversimplify the complex nature of the disorder. Alternatively, the subtyping approach can characterize the individual variation and delineate relatively homogenous subgroups within the disorder, providing greater insight into the clinical characteristics and enabling more precise diagnoses. For instance, the previous study identified three novel types of ADHD, known as mild, surgent, and irritable (Karalunas et al., 2014). Specifically, the mild type is characterized by normal emotional regulation, while the surgent type is marked by extremely high levels of positive approach motivation. On the other hand, the irritable type is characterized by negative emotionality and increased levels of anger. Studies on other neurodevelopmental disorders have also demonstrated the efficacy of dissecting heterogeneity within disorders. For example, Mihailov et al.

(2020) found three distinct behaviorally clustered autistic subgroups (i.e., emotion, attention, anxiety/depression) and their related cortical signatures using 1,093 participants from healthy brain network cohort (Mihailov et al., 2020). Hong et al. (2018) also discovered three distinct neuroanatomical subtypes in a large cohort of individuals with ASD (Hong et al., 2018). Interestingly, the study demonstrated that the subtyping approach improved the prediction performance of total symptom scores in a single subject. These findings suggest that dissecting the heterogeneity with the subtyping approach could decrease the inter-subject variability associated with the disorder.

1.2. Purpose of Research

The heterogeneity of symptoms and brain pathophysiology among individuals with ADHD is a major challenge in accurate diagnosis and effective treatment. To address this issue, this study aims to dissect the heterogeneity in ADHD leveraging gray matter morphometric and white matter microstructure estimates in prepubertal children. Then, this study aims to characterize whether each ADHD subgroup has distinct behavioral and brain characteristics. Finally, this study aims to investigate how these characteristics change with age. Unpacking the brain heterogeneity of ADHD could offer a more comprehensive understanding of the shared and unique traits of ADHD across subgroups. Furthermore, delving into the dissimilarities in developmental trajectories among the dissected subgroups could provide knowledge of the heterogeneity of ADHD and its brain development.

2. Materials and Methods

2.1. Participants

This study included 11,878 developing children aged 9-10 years from the Adolescent Brain and Cognitive Development (ABCD) study. The ABCD study is the largest long-term study of brain development and child health in the United States (Jernigan et al., 2018). Participants were recruited across 21 research sites. Participants provided informed consent and assent to the ABCD study. Following the acquisition of the data from the ABCD study, all experimental protocols for current data analysis were approved by Seoul National University's institutional review board (IRB). I obtained the ABCD release 4.0 datasets from the National Institute of Mental Health (NIMH) Data Archive. When data was unavailable in the said version, I used the release 2.0 or 3.0 version. After preprocessing, 10,152 participants (ADHD group: N=173, non-ADHD group: N=9,979) were used for the final analysis (**Figure 2**).

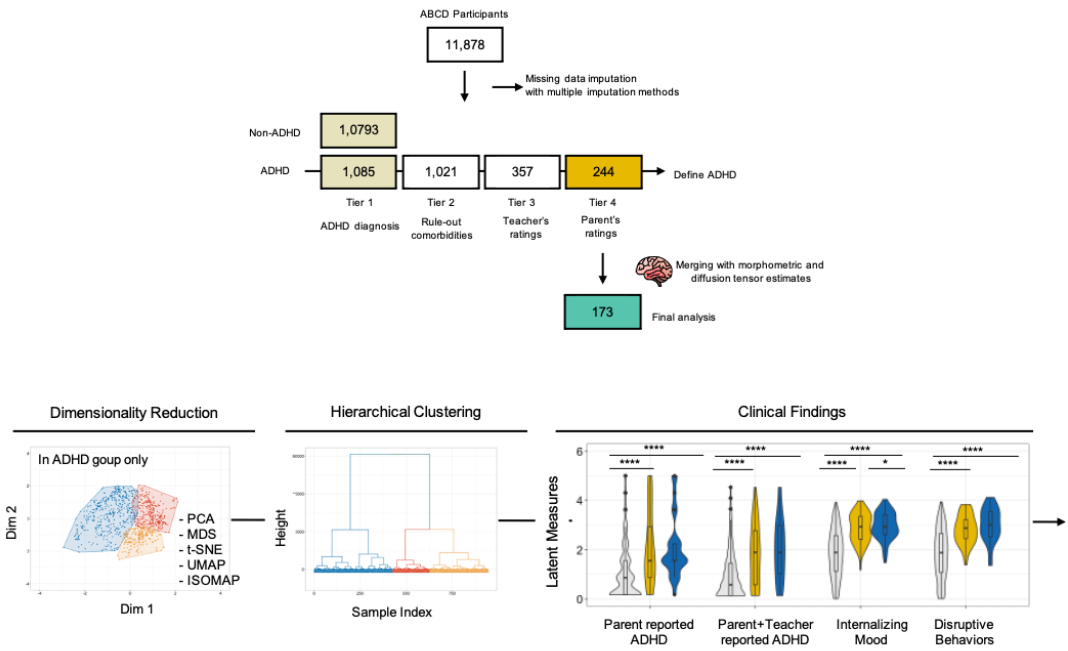

Figure 2. Data analysis schematic.

2.2. Attention-deficit/hyperactivity disorder (ADHD)

The baseline categorical diagnosis and symptoms of ADHD assessment were obtained from the computerized Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-COMP) for DSM-5 (Kaufman et al., 1997), which has been widely used for diagnosing mental disorders (Findling et al., 2014; Findling et al., 2008; Robb et al., 2010; Townsend et al., 2020), including ADHD (Bernanke et al., 2022; Santisteban et al., 2014; Schulz et al., 2010). In addition to using K-SADS-COMP, I performed additional diagnostic steps, as previously described (Cordova et al., 2022). The detailed procedures are outlined in **Table 1**, in accordance with DSM-5 criteria.

Table 1. ADHD assessment according to DSM-5 criteria.

Tiers	Description
Tier 1	Met present ADHD diagnosis (*DSM-5* criterion A) as indicated by the parent-reported KSADS-COMP
Tier 2	ADHD Tier 1 + rule-out comorbidities (*DSM-5* criterion E) • Intellectual development disorder (IDD) estimated IQ < 70 • Bipolar disorder (bipolar-I presently manic and a depressive disorder) • Unspecified schizophrenia spectrum and other psychotic disorders
Tier 3	ADHD Tier 2 + teacher's ratings (*DSM-5* criterion C) of attention T scores ≥ 65 using the teacher-report Brief Problem Monitor (BPM)
Tier 4	ADHD Tier 3 + parent's ratings (*DSM-5* criterion E) of Child Behavior Checklist (CBCL) attention scale T scores ≥ 65 or ADHD *DSM-5* scale T scores ≥ 65

2.2.1. ADHD assessment

Tier 1: KSADS-COMP ADHD. The starting point of the criterion was to determine if the child had present ADHD as indicated by the parent-reported KSADS-COMP. *Tier 2: Rule out comorbidities*. For the ADHD diagnosis, the symptoms of ADHD should not be better attributed to any other mental disorders (American Psychiatric Association & Association, 2013). Therefore, I ruled out alternative causes of ADHD symptoms identified by the ADHD-MHM-QC as follows: (1) intellectual disability, (2) bipolar disorder, and (3) unspecified schizophrenia spectrum and other psychotic disorders. First, I excluded intellectual development disorder (IDD)

with IQ screen measures, using the NIH Toolbox WISC-V Matrix Reasoning scale score ≤ 3, which approximately indicates IQ ≤ 70. (Cordova et al., 2022). Then, I ruled out bipolar disorder due to its manifesting similarities with ADHD and mania. For estimations of bipolar disorder, I used both parent and youth versions of KSADS-COMP. Finally, I excluded the unspecified schizophrenia spectrum and psychotic disorders. This is because psychotic symptoms are similar to inattention, even though the two are distinct disorders (Olde Loohuis et al., 2021). Psychotic disorders were assessed with KSADS-COMP.

Tier 3: Teacher's rating in the school setting. DSM-5 clearly states that ADHD symptoms should be observed in various contexts, such as the home and school; however, the current KSADS-COMP from the ABCD study does not consider contexts. Thus, I additionally used the teacher's attention T scores of the Brief Problem Monitor (BPM) measurement. Since the BPM measurement had a number of missing values, I performed additional multiple imputations (see **"2.4. Missing data imputation"**).

Tier 4: Parent's rating for additional information. Beyond a clinical interview, assessing whether the attention problem is out of the ordinary for the child's age is important. To this end, I used the parent's Child Behavioral Checklist (CBCL) attention or ADHD DSM-5 scale with a recommended clinical cutoff of 65 (Bernanke et al., 2022).

2.2.2. Comorbid disorders

Investigating the presence of comorbid mental disorders among children with ADHD is of the utmost importance for preventing any external confounders. Therefore, I examined the association between ADHD and its comorbidities. The included comorbid psychiatric disorders in the study were (1) disruptive disorders (oppositional defiant disorder (ODD), conduct disorder (CD)), (2) fear disorders (agoraphobia, panic disorder, specific phobia), (3) anxiety disorders (generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), separation anxiety, social anxiety, unspecified anxiety

disorder (Unspec. AD), any fear or anxiety disorder)), and (4) mood disorders (major depressive disorder (MDD), disruptive mood dysregulation disorder (DMDD), unspecified depressive disorder (Unspec. DD), or any mood disorder) (Mohammadi et al., 2021). All the disorders were estimated using parent and child versions of KSADS-COMP, except for ODD/CD composite scores (**Table 2**). ODD/CD composite scores were measured with BPM scales.

Table 2. Definitions of comorbid disorders of ADHD.

Measure		Description
Disruptive Disorders	ODD (P)	Met present ODD diagnosis by the KSADS-COMP
	CD (P)	Met present CD diagnosis by the KSADS-COMP
Fear Disorders	Agoraphobia (P)	Met present agoraphobia by the KSADS-COMMP
	Panic disorder (P)	Met present panic disorder diagnosis by the KSADS-COMP
	Specific phobia (P)	Met present specific phobia diagnosis by the KSADS-COMP
Anxiety Disorders	GAD (P/Y)	Met present generalized anxiety disorder by the KSADS-COMP
	PTSD (P)	Met present post-traumatic stress disorder or other specified trauma-and stressor-related disorder by the KSADS-COMP
	OCD (P)	Met present obsessive-compulsive disorder by the KSADS-COMP
	Separation anxiety (P)	Met present separation anxiety disorder by the KSADS-COMP
	Social anxiety (P/Y)	Met present social anxiety disorder by the KSADS-COMP
	Unspec. AD (P/Y)	Met other specified anxiety disorders by the parent version of the KSADS-COMP or the youth version of the KSADS-COMP
Mood Disorders	MDD (P/Y)	Met present major depressive disorder by the KSADS-COMP
	DMDD (P/Y)	Met present disruptive mood dysregulation disorder by the KSADS-COMP
	Unspec. DD (P/Y)	Met present unspecified depressive disorders by the KSADS-COMP

Note, P=parent report, Y=youth report, P/Y=parent and/or youth report

2.2.3. Medication treatment

To investigate the association between ADHD and medication status, the medication prescription status of children was examined using data from the PhenX instrument. Caregivers were asked to provide information on whether the medication had been taken within the last two weeks. Based on the subjective responses, I additionally coded the medication status as binary (yes or no). Here, methylphenidate derivatives, amphetamine derivatives, α-2-agonists, and atomoxetine (**Table 3**) were considered ADHD medications (Shoval et al., 2021).

Table 3. Definitions of ADHD medications.

Drug Class	Active Compound(s)	Medication
Methylphenidate Derivative (MPH)	Methylphenidate HCl	Ritalin
		Quillivant
		Quillichew
		Methylin
		Concerta
		Metadate
		Aptensio
		Daytrana
	Dexmethylphenidate HCl	Focalin
Amphetamine (AMPH)	Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, Amphetamine Sulfate	Adderall
		Adzenys
		Dynavel
		Evekeo
	Dextroamphetamine Sulfate	Zenzedi
		Dexedrine
		Procentra
	Lisdexamfetamine Dimesylate	Vyvanse
Alpha Agonist	Guanfacine	Intuniv
	Guanfacine HCl	Tenex
	Clonidine HCl	Catapres
		Nexiclon
Atomoxetine	Atomoxetine HCl	Strattera

2.3. Neuropsychological measures

2.3.1. Cognitive measures

The cognitive measures were obtained from the ABCD study's NIH Toolbox (Luciana et al., 2018), Little Man Test (Acker & Acker, 1982), and Pearson Rey Auditory Verbal Learning Test (RAVLT) (Strauss et al., 2006). The NIH Toolbox measures cognitive abilities essential for successful functioning throughout life (Bleck et al., 2013; Gershon et al., 2013; Hodes et al., 2013; Luciana et al., 2018). Among the NIH Toolbox subscales, I used the following subscales: Picture Vocabulary, Oral Reading, List Sort Working Memory, Flanker, Dimensional Change Card Sort, Pattern Comparison Processing Speed, and Picture Sequence Memory. Second, the Little Man Test measures visuospatial processing flexibility and attention. For the Little Man Test, I calculated the correct percentage of the 32 trials the Little Man Test. Lastly, the RAVLT test measures verbal learning and memory. For RAVLT, I calculated the sum of the correct short delay trials 1-5. Additionally, I constructed the general ability, executive function, and learning/memory components (**Table 4, Figure 3**) (Thompson et al., 2019) using structural equation modeling (comparative fit index (CFI)= .974, root mean square error of approximation (RMSEA)= .048).

Table 4. Definitions of cognitive measures.

Measure	Description
General Cognitive Ability	Picture Vocabulary, Oral Reading, List Sort Working Memory Test from the NIH Toolbox, and correct percentage of provided 32 trials from the Little Man Test
Executive Function	Flanker, Dimensional Change Card Sort, Pattern Comparison Processing Speed Task from the NIH Toolbox
Learning and Memory	Picture Sequence Memory Task, List Sort Working Memory Task from the NIH Toolbox, and the sum of correct short delay trials 1-5 from the RAVLT

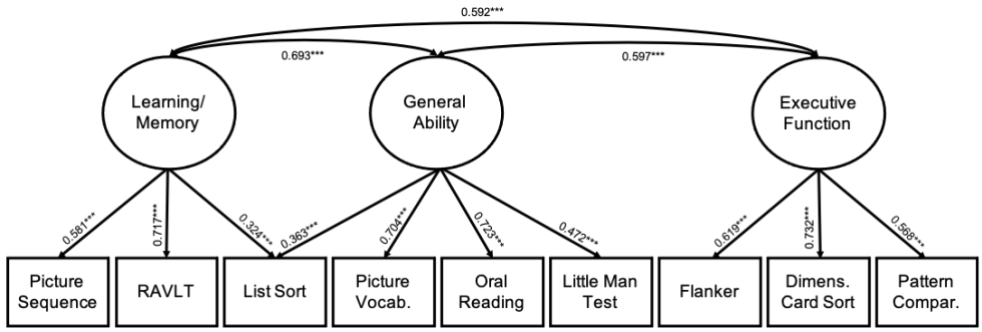

Figure 3. Confirmatory factor analysis (CFA) model for latent cognitive variables. Note, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$

2.3.2. Behavioral measures

Using the CBCL and KSADS-COMP, I determined irritability, internalizing, and externalizing scores (**Table 5**). First, I calculated irritability scores by taking the average standardized scores from five parent CBCL items and three ODD symptom items from the KSADS-COMP. Second, I used the CBCL Syndrome Scale (t-score) for internalizing and externalizing scores. As in a previous study (Cordova et al., 2022), I additionally evaluated each behavioral composite's validity by constructing latent variables (Disruptive behavior disorder, CFI=1.000, RMSEA= .029; Irritability, CFI= .988, RMSEA= .081; Internalizing, CFI= .995, RMSEA= .066) (**Figure 4**).

Table 5. Definitions of behavioral measures.

Measure	Description
Irritability	CBCL measures: stubborn, sullen, or irritable temper tantrums or hot temper, sudden changes in mood or feelings, sulks a lot, and argues a lot; KSADS-COMP measures: often loses temper, often touchy or easily annoyed, and often angry or resentful
Internalizing	Internal CBCL Syndrome Scale (t-score)
Externalizing	External CBCL Syndrome Scale (t-score)

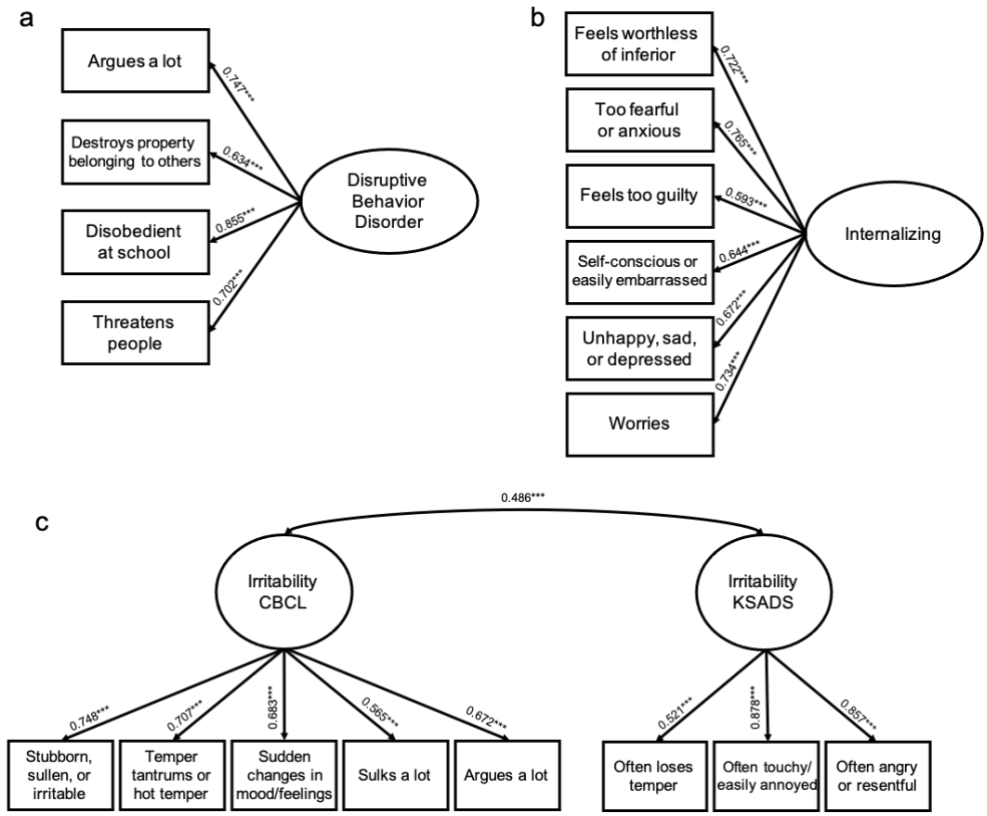

Figure 4. Confirmatory factor analysis (CFA) model for latent behavioral variables. a, Disruptive behavior disorder latent variable. **b**, Internalizing behavior latent variable**. c,** Irritability latent variable**. Note,** **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$

2.4. Missing data imputation

In preprocessing our datasets, I found that the teacher's attention T scores had a large amount of missingness (66.63%). To address this problem, I performed multiple imputations (Enders, 2010, 2017; Little et al., 2014; McCartney & Burchinal, 2006; Schafer & Graham, 2002; Van Buuren, 2018). For the multiple imputations, I adopted the overall procedures from a previous study (Cordova et al., 2022), which validated the BPM imputation results. To control for potential

confounding effects, I additionally included basic demographic variables in the algorithms: age, sex, race, parental income, parental marital status, and race/ethnicity. Due to causing model errors, research sites were excluded from the multiple imputation model. To this end, I generated one hundred imputed data sets based on the Bayesian model-based estimates of missing values. For each dataset, I analyzed and pooled the results using standard adjustments, thus preventing the shrinkage of standard errors and providing the most accurate data explanation. To validate the results of the imputed dataset, I confirmed the distribution of the imputed datasets across Tier 1 - 4 (**Table 6**). In particular, I applied the missing at random (MAR) and predictive mean matching (PMM) methods (Enders, 2010; Murray, 2018; Van Buuren, 2018). When I pooled the final results, I averaged the parameter estimates according to Rubin's rules (Van Ginkel et al., 2020).

2.5. MRI data acquisition and processing

2.5.1. Structural magnetic resonance imaging (sMRI)

T1-weighted (T1w) and T2-weighted (T2w) 3D structural images were acquired and preprocessed from the ABCD study. The ABCD Data Analysis, Informatics and Resource Center (DAIRC) performed the main processing and analysis of MRI data for the following procedures using FreeSurfer version 7.1.1: skull-stripping (Ségonne et al., 2004), white matter segmentation (Dale et al., 1999), initial mesh creation (Dale et al., 1999), topological defection correction, surface optimization (Dale et al., 1999), and nonlinear registration to a spherical surface-based atlas (Fischl, Sereno, Tootell, et al., 1999). Next, Desikan-Killiany atlas-based labels (Desikan et al., 2006) and atlas-based segmentation labels were allocated to the cortical and subcortical structures. The cortical and subcortical structure comprises 68 and 30 regions, respectively. Finally, I used a total of 770 variables of cortical and subcortical regional volume, cortical thickness (Fischl & Dale, 2000), cortical area (Chen et al., 2012; Joyner et al., 2009), and sulcal depth (Fischl, Sereno, & Dale, 1999).

2.5.2. Diffusion magnetic resonance imaging (dMRI)

The diffusion magnetic resonance imaging (dMRI) data were obtained and preprocessed from the ABCD study. The DAIRC processed the images for the following protocols: eddy current distortion correction, head motion correction, diffusion gradients adjustment, robust diffusion tensor estimation, B0 distortion correction, T1w image registration, and resampling. The detailed descriptions for dMRI preprocessing are outlined in the ABCD Release Notes. Applying the MRtrix3 (Tournier et al., 2019), diffusion estimates were measured by using FA, MD, longitudinal (or axial) diffusivity (AD), and transverse (or radial) diffusivity (RD). These metrics measure the magnitude and direction of water diffusion, reflecting the organization of axons and myelin sheath (Chang et al., 2017; Damatac et al., 2022; Seehaus et al., 2015). In particular, FA represents the degree of anisotropy of water molecules, with values ranging from 0 (isotropic movement) to 1 (anisotropic movement) (Curran et al., 2016). It reflects the directional preference of water diffusion in each voxel. MD, on the other hand, is the average molecular motion, calculated by the overall mean squared displacement of the water molecules (Curran et al., 2016). A decrease in FA and an increase in MD occur when barriers to water diffusion weaken, for example, due to the degeneration of structured (Stebbins, 2010). Among four metrics, we focus on the FA and MD of white matter tracts, the most commonly studied metrics.

2.5.3. Quality assessment and control

To ensure the quality of brain imaging data, I conducted quality assessments using ABCD DAIRC's imaging pipeline (Hagler et al., 2019). I employed the recommended imaging inclusion criteria, which encompasses all quality control (QC) criteria satisfying (e.g., T1/T2 series passed raw QC, FreeSurfer QC, and derived results availability) each data type. The detailed inclusion criteria are available in the ABCD Release Notes, named 'MRI QC and Recommended Image Inclusion Criteria.' The ABCD DAIRC's pipeline has three stages for quality assessment. First, the ABCD DAIRC staff manually reviewed series that did not

follow the protocol, verifying whether the key imaging parameters, such as voxel size or repetition time, were consistent with the expected values for the particular scanner. Additionally, for dMRI, the B0 distortion field map series was checked. Second, quality assessment was automatically conducted, calculating the mean and standard deviation of brain values and spatial signal-to-noise ratio (SNR) for sMRI, and the average motion with framewise displacement and the number of slices and frames affected by abrupt head motion for dMRI. Third, data quality was assessed using a binary score (0 or 1). A score of 0 indicates that the images have severe flaws, such as blurring or ghosting due to motion artifacts, and a score of 1 indicates that the images are acceptable. Finally, the sMRI data that passed QC comprised 10,739 participants, while the dMRI data had 10,407 participants.

2.6. Genetic data acquisition and processing

2.6.1. Genotype data

With Rutgers University Cell and DNA Repository (RUCDR), and using Affymetrix NIDA SmokeScreen Array (Baurley et al., 2016), the ABCD study collected and genotyped the DNA in saliva samples consisting of 733,293 single nucleotide polymorphisms (SNPs). The RUCDR implemented QC for DNA by examining the calling signals and variant call rates (<95% removed). In this regard, all SNPs had an adequate call rate (>94%). The ABCD DAIRC additionally performed the QC process following the Ricopili pipeline (Lam et al., 2020). Finally, the QC-passed genotype data was presented in binary PLINK format, containing 11,099 unique individuals and 516,598 genetic variants. Following the generation of the Log R Ratio (LRR) and B Allele Frequencies (BAF) (Kendall et al., 2017), the genotype data were imputed with TOPMed reference, including allele frequencies calculation, the Haplotype Reference Consortium (HRC) - 1000 Genomes - check execution, and VCF files conversion using PLINK v1.9. Non-genotype autosomal SNPs were imputed with 1000G phase 3 only when the SNPs had a high level of confidence (INFO ≥ .8).

2.6.2. Genetic relatedness inference

To address potential population stratification resulting from genetic relatedness and ancestry admixture, extra QC processes were performed (Joo et al., 2022) accounting for the diverse ethnic backgrounds and genetic ancestries of the ABCD participants. The genetically unrelated individuals were determined using the *SNPRelate* R package, and their genotype data's ancestrally informative principal components (PCs) were calculated (Zheng et al., 2017; Zheng et al., 2012). The PC-Air algorithms found familial or cryptic relatedness as robust principal components. First, using the KING-robust algorithm, pairwise kinship coefficients were estimated from a pruned set of independent genetic variants with a linkage disequilibrium (LD) threshold of $r^2 < .1$. After excluding the genetically related individuals with closer than 3rd-degree relatedness (kinship threshold=$2^{(-4.5)}$), one individual per related pair was only held onto. To achieve this, PC-Air was used to identify 8,845 unrelated individuals and compute their genotype data's PC. A second round of PC was performed to calculate the genotype data more accurately with updated unrelated individuals. As a result, 88 participants who showed greater than six standard deviations in the Mahalanobis distances were excluded. Finally, 8,620 genetically-unrelated participants were obtained.

2.6.3. Genome-wide polygenic scores (GPSs)

To evaluate the polygenic effects of ADHD-related traits, the GPSs were constructed using publicly available GWAS summary statistics. The GPS provides a single score representing an individual's genetic liability to a particular trait, taking into account the polygenic effect of the trait (Wray et al., 2007). The GPS of each trait is calculated by adding up the total number of alleles (j) for a particular SNP in individual (i), and multiplying it by the SNP's effect size (β) obtained from GWAS conducted on a different discovery population (Li & He, 2021).

$$GPS = \Sigma\, SNP_{ij}\, \beta_j$$

To estimate the SNP effect size shared between summary statistics and LD diversity, PRS-CSx software, a Bayesian polygenic modeling and prediction framework based on a python-based command line tool (Ruan et al., 2022) was employed. Then, the polygenic scores were calculated using PLINK version 1.9 (Purcell et al., 2007). Finally, four values of hyperparameters φ (i.e., 10^{-6}, 10^{-4}, 10^{-2}, and 1) were evaluated with linear combination models on trait-related phenotypes (Ruan et al., 2022) for each GPS trait separately. The linear models included covariates of sex, age, genetic ancestry, and the first ten ancestrally informative PCs to prevent potential confounding effects. The best φ value of GPSs was selected, considering both R^2 and beta coefficients. The included GPSs traits are genetically related to ADHD or show high comorbidities with ADHD (Demontis et al., 2019): ADHD, anorexia nervosa, anxiety, autism spectrum disorder, bipolar disorder, body mass index (BMI), cognitive performance, cross disorder, depressive symptoms, educational attainment, major depressive disorder (MDD), neuroticism, impulsivity (e.g., automobile speeding propensity), IQ, risky behaviors, schizophrenia, substance use (alcohol dependence, alcohol use, ever smoker), and subjective wellbeing.

2.7. Dissecting the heterogeneity of the brain structure in ADHD

2.7.1. Dimensionality reduction

A subset of whole-brain features would uncover biologically significant ADHD features (Drysdale et al., 2017; Lin et al., 2018). Therefore, to select the features that are most predictive of the ADHD brain, I reduced the dimensionality of the brain. For optimal dimensionality reduction, I tested and compared various methods: principal component analysis (PCA), multidimensional scaling (MDS), t-distributed stochastic neighbor embedding (t-SNE), independent component analysis (ICA), uniform manifold approximation and projection (UMAP), and isometric mapping (ISOMAP).

2.7.2. Agglomerative hierarchical clustering analysis

To dissect the heterogeneity of the structural brain in ADHD, I performed an agglomerative hierarchical clustering analysis. This method, which is based on Ward's minimum variance approach (Ward Jr, 1963), calculates a dissimilarity matrix and assigns each subject to pairs of subjects in the closest proximity (Drysdale et al., 2017). The optimal number of clusters was determined using the Calinski-Harabasz (CH) index, with 10 classes (k = 1~10) estimated (Hong et al., 2018). As defined by the CH index, a higher value indicates that the clusters are dense and well-defined (Caliński & Harabasz, 1974). Before the clustering was carried out, all brain features underwent vertex-wise z-scoring to normalize them, as each brain metric has a unique scale (e.g., FA has a scale ranging from 0 to 1). I conducted a bootstrap-based stability test with 1,000 iterations to validate the results.

2.8. Relation to ADHD subgroups and neuropsychological measures

To investigate the link between ADHD subgroups and neuropsychological measures, I compared the cognitive, behavioral, and brain characteristics across each newly identified ADHD subgroup. Statistical analysis was performed using a combination of one-way Analysis of Covariance (ANCOVA) and chi-square tests for continuous and categorical dependent variables, respectively. Post hoc pairwise t-tests were conducted to determine group differences. To account for multiple comparisons, a False Discovery Rate (FDR) correction was applied, and only those results with a significance level of less than .05 were selected. The statistical models were controlled for the following covariates: age, sex, parental income, parental marital status, research sites, and race/ethnicity.

3. Results

3.1. Demographic characteristics

I assessed the demographic characteristics of the ADHD evaluation criteria to determine the accuracy of the ADHD group designation. The prevalence was 9.137% based on the KSADS-COMP criteria only (Tier 1), 8.599% after ruling out comorbidities (Tier 2), 3.006% with teacher's ratings (Tier 3), and 2.057% after additional parental reports with CBCL (Tier 4). The sex distribution of the overall sample remained similar across all four tiers, but as the criteria became more stringent, the ADHD group showed lower general cognitive ability and ADHD GPS scores and higher scores for problem behaviors (**Table 6**). These changes across the convergent validity measures were statistically significant and correlated with ADHD-related composite scores.

Table 6. Demographic characteristics across ADHD assessment.

Variables	Full sample N=11,878	Non-ADHD N=10,793	ADHD Tier 1 N=1,085	ADHD Tier 2 N=1,021	ADHD Tier 3 N=357	ADHD Tier 4 N=244
Prevalence (%)	-	-	9.137	8.599	3.006	2.057
Age (months)	118.979 (0.069)	119.015 (0.072)	118.627 (0.226)	118.567 (0.234)	118.292 (0.481)	117.941 (0.550)
Sex (Male, %)	52.159	50.424	69.334	69.096	69.551	69.014
Income group (1-10)	7.119 (0.023)	7.128 (0.025)	7.021 (0.077)	7.152 (0.077)	6.676 (0.175)	6.537 (0.192)
Race (%)						
White	52.046	51.857	53.848	55.437	36.987	46.001
Black	15.022	14.861	16.597	15.555	19.216	19.711
Hispanic	20.299	20.727	15.991	15.292	18.584	19.075
Asian	2.124	2.263	0.793	0.785	0.729	0.596
Others	10.508	10.274	12.824	12.931	13.792	14.618
Married status (%)						
Married	67.525	67.856	61.874	65.748	58.285	56.624
Widowed	0.828	0.771	1.211	1.286	1.361	0.733
Divorced	9.198	9.148	8.989	9.551	10.088	8.731
Separated	3.970	3.963	3.656	3.885	5.280	5.397
Never married	12.591	12.359	12.864	13.669	18.159	20.16
Living with partner	5.880	5.877	5.508	5.853	6.824	8.354
Cognitive measures						
General cognitive ability	-0.003 (0.003)	0.005 (0.003)	-0.083 (0.010)	-0.070 (0.010)	-0.157 (0.023)	-0.170 (0.024)
Executive function	-0.005 (0.005)	0.010 (0.005)	-0.158 (0.017)	-0.138 (0.017)	-0.258 (0.042)	-0.280 (0.046)
Learning and memory	0.0001 (0.005)	0.015 (0.005)	-0.145 (0.016)	-0.126 (0.016)	-0.266 (0.036)	-0.293 (0.038)
CBCL measures						
Attention T score	53.902 (0.057)	52.790 (0.044)	64.967 (0.267)	64.645 (0.267)	67.785 (0.632)	71.784 (0.576)
Internalizing T score	48.446 (0.098)	47.579 (0.098)	57.070 (0.328)	56.753 (0.336)	58.069 (0.680)	60.649 (0.761)
Externalizing T score	45.723 (0.095)	44.611 (0.092)	56.783 (0.333)	56.390 (0.340)	59.534 (0.754)	62.063 (0.747)
ADHD GPS	0.108 (0.163)	0.099 (0.165)	0.201 (0.148)	0.192 (0.143)	0.256 (0.157)	0.267 (0.155)

Note, The provided values are pooled mean and standard error estimates across all imputation sets (see **"2.4. Missing data imputation"**).

3.2. Dissecting the heterogeneity of the ADHD brain

I performed an unsupervised clustering analysis to examine the heterogeneity of brain morphometric and white matter microstructural tissue properties in the ADHD group from Tier 4. To manage the challenge of high dimensionality and data complexity, dimensional reduction techniques were applied before clustering the brain features. The optimal number of clusters was determined using the CH index, and the cluster validity was evaluated with an average silhouette width score. The UMAP method was chosen as the main analysis tool, as it yielded the highest silhouette width score (average score: .82) (**Figure 5**). The newly identified subgroups were named 'ADHD-#' based on the number of subgroups, and the control group was referred to as 'non-ADHD'. Through the use of five different dimensional reduction methods, the clustering model showed that ADHD children could be separated into two distinct subgroups using brain data, with two being the optimal number of clusters.

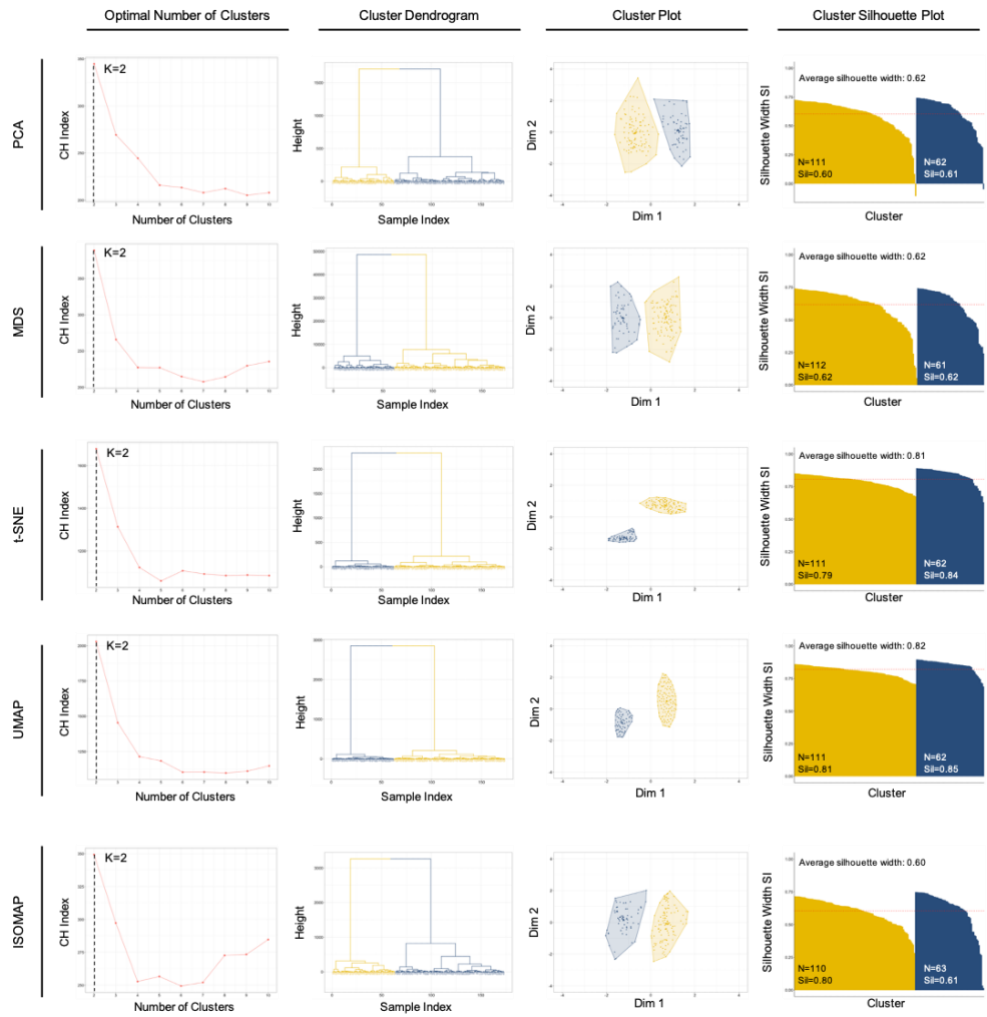

Figure 5. Unsupervised clustering model with ADHD brain. Across five different dimensional reduction techniques (PCA, MDS, t-SNE, UMAP, and ISOMAP), the unsupervised clustering model optimally detected two subgroups (ADHD-1 and ADHD-2). The optimal number of clusters was determined through the CH index, which assesses the similarity of each cluster in comparison to the other clusters. The optimal value of *k* was found by evaluating values ranging from 1 to 10. After clustering the brain with the optimal *k*, I further assessed the clustering validity by computing the silhouette coefficient, which measured each participant's mean intra-cluster distance and the mean nearest-cluster distance.

3.3. Relation to ADHD subgroups and demographic, cognitive and behavioral measures

I investigated the relationship between brain structure differences in ADHD subgroups and demographic, cognitive, and behavioral patterns. Demographic differences were found in sex, parental marital status, and parental income, with the greatest difference being between the non-ADHD group and ADHD-1 (**Figure 6**). The KSAD symptom scores showed that individuals with ADHD-1 and ADHD-2 scored higher in total, hyperactivity/impulsivity, and inattention symptoms compared to those without ADHD (total ADHD, F=906.721, P_{fdr}< .001; hyperactivity/impulsivity, F=910.832, P_{fdr}<.001; inattention, F=744.774, P_{fdr}< .001) (**Table 7, Figure 7. a-c**). The results of cognitive and behavioral measurements revealed distinct characteristics in both ADHD-1 and ADHD-2 groups compared to non-ADHD, however, no significant differences were found between ADHD-1 and ADHD-2 (**Figure 7. d-g**). Specifically, the results of the pattern comparison task (P_{fdr}= .020) and flanker test (P_{fdr}= .002) showed only significant impairments in ADHD-1 and ADHD-2 groups to non-ADHD, respectively (**Figure 7. d**). Additionally, the internalizing mood latent composite showed a higher score in ADHD-2 compared to non-ADHD and ADHD-1 (F=61.742, P_{fdr}< .018) (**Figure 7. g**). The proportions of ADHD comorbidities, ODD, GAD, and OCD, were also different between non-ADHD and each ADHD subgroup, with only non-ADHD vs. ADHD-2 showing significant differences in MDD (**Figure 8**).

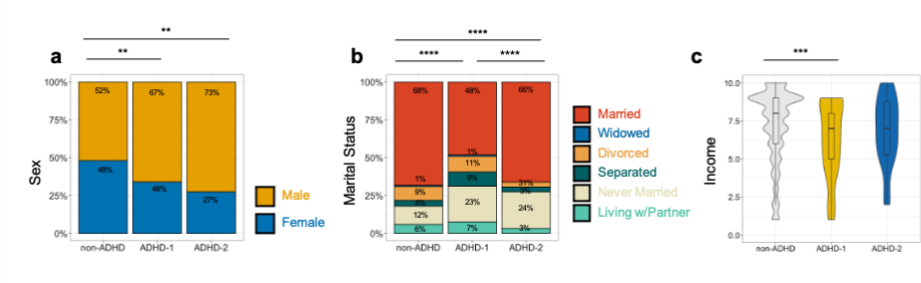

Figure 6. Proportion differences in demographic data across ADHD subgroups. a, Sex distribution. **b**, Marital status distribution. **c**, Parental income levels. **Note,** FDR-corrected post hoc test, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$

Table 7. Clinical characteristics across subgroups.

Variable	Non-ADHD (N=10,705)	ADHD 1 (N=111)	ADHD 2 (N=63)	*F* (P_{fdr})
Total symptom scores	1.56 ± 0.0004	16.7 ± 0.031	17.2 ± 0.052	906.721 ***
Hyperactivity/Impulsivity	0.63 ± 0.0002	7.69 ± 0.024	7.81 ± 0.044	910.832 ***
Inattention	0.93 ± 0.0002	8.98 ± 0.018	9.37 ±0.028	744.774 ***

Note, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$

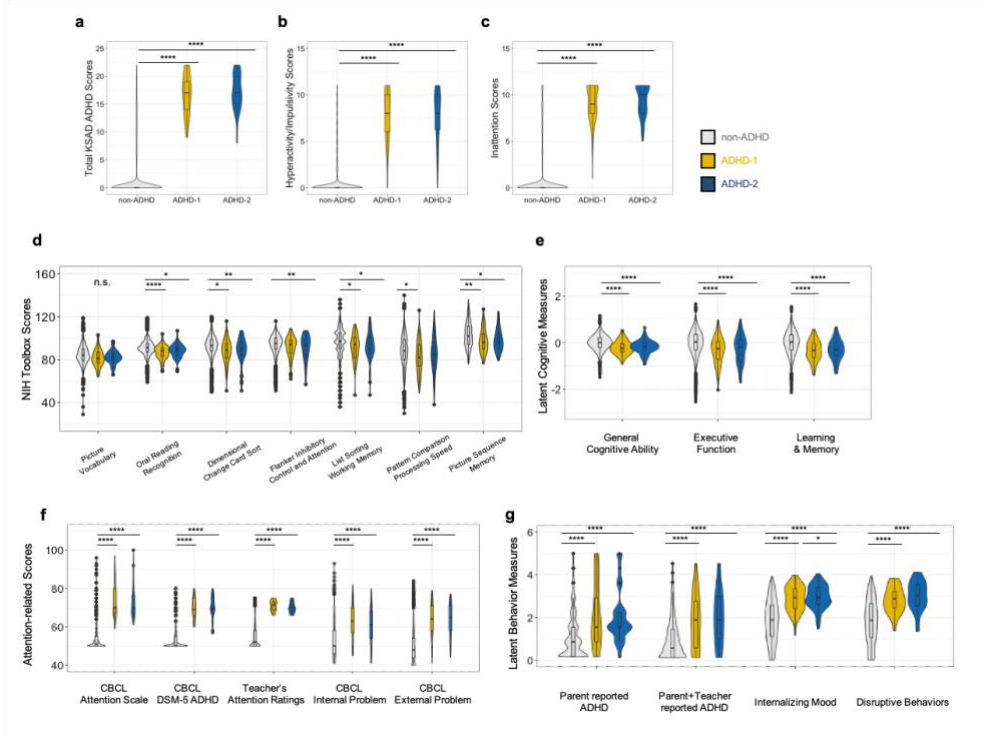

Figure 7. Clinical findings across ADHD subgroups. a, KSAD total ADHD symptom scores. **b**, KSAD hyperactivity/impulsivity scores. **c**, KSAD inattention scores. **d,** NIH Toolbox cognition battery scores. **e**, Latent cognitive variables (general ability, executive function, and learning and memory). **f**, CBCL-based problem behaviors. **g**, Latent variables of attention problems and comorbidities of ADHD. **Note,** FDR-corrected post hoc test, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$

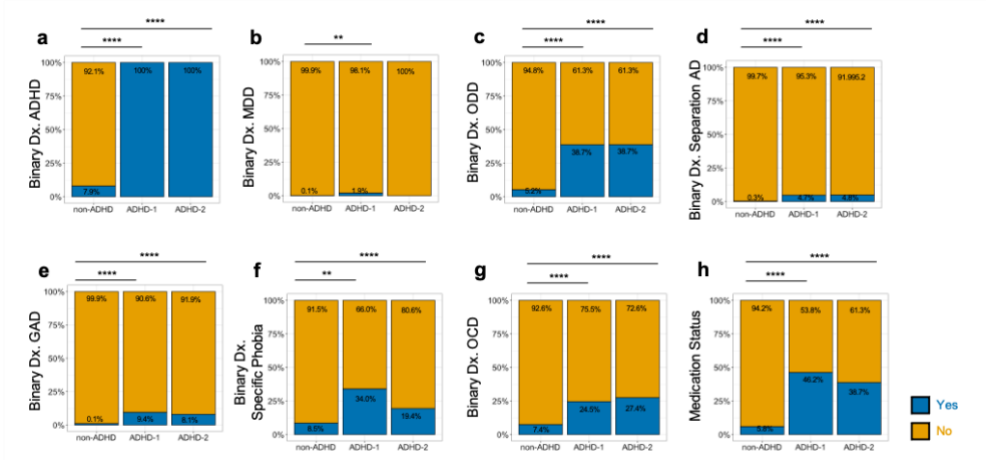

Figure 8. Comorbidities proportion and medication status across ADHD subgroups. **a**, Diagnosis of present attention-deficit/hyperactivity disorder (ADHD). **b**, Diagnosis of present major depressive disorder (MDD). **c**, Diagnosis of present oppositional defiant disorder (ODD). **d**, Diagnosis of present separation anxiety disorder. **e**, Diagnosis of a present general anxiety disorder (GAD). **f**, Diagnosis of present specific phobia. **g**, Diagnosis of present obsessive-compulsive disorder (OCD). **h**, Medication status. **Note,** The evaluations were conducted using the KSADS assessment, which assigns a binary score (0 for absence and 1 for the present) to each measurement. Parents provided all these reports. The current KSADS binary measurement for ADHD does not consider functional impairment in multiple environments. FDR-corrected post hoc test, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$

3.4. Relation to ADHD subgroups and GPS measures

Regarding GPSs, the analysis was carried out respectively for European-filtered and multi-ancestry data. In European ancestry (**Figure 9**), the GPSs of bipolar disorder (F=3.602, P_{fdr}=.027), BMI (F=5.051, P_{fdr}=.006), and risk tolerance (F=3.564, P_{fdr}=.028) were associated with differences across ADHD subgroups. The GPS for bipolar disorder (P_{fdr}=.033) in the ADHD-2 subgroup was significantly higher compared to ADHD-1. Additionally, ADHD-2 showed higher GPSs of BMI (P_{fdr}=.011) and risk tolerance (P_{fdr}=.046) than non-ADHD individuals, while ADHD-1 showed no significant differences. In line with the findings in European ancestry, the results with multi-ancestry also showed a similar tendency in bipolar disorder (F=3.075, P_{fdr}=.046) (**Figure 10**). However, the multi-ancestry analysis did not find significant differences in BMI and risk tolerance. Instead, the multi-ancestry analysis showed higher lifetime cannabis use (F=4.493, P_{fdr}=.011) when comparing ADHD-1 and ADHD-2, and lower educational attainment (F=5.871, P_{fdr}=.003) when comparing non-ADHD and ADHD-2 (**Figure 10**).

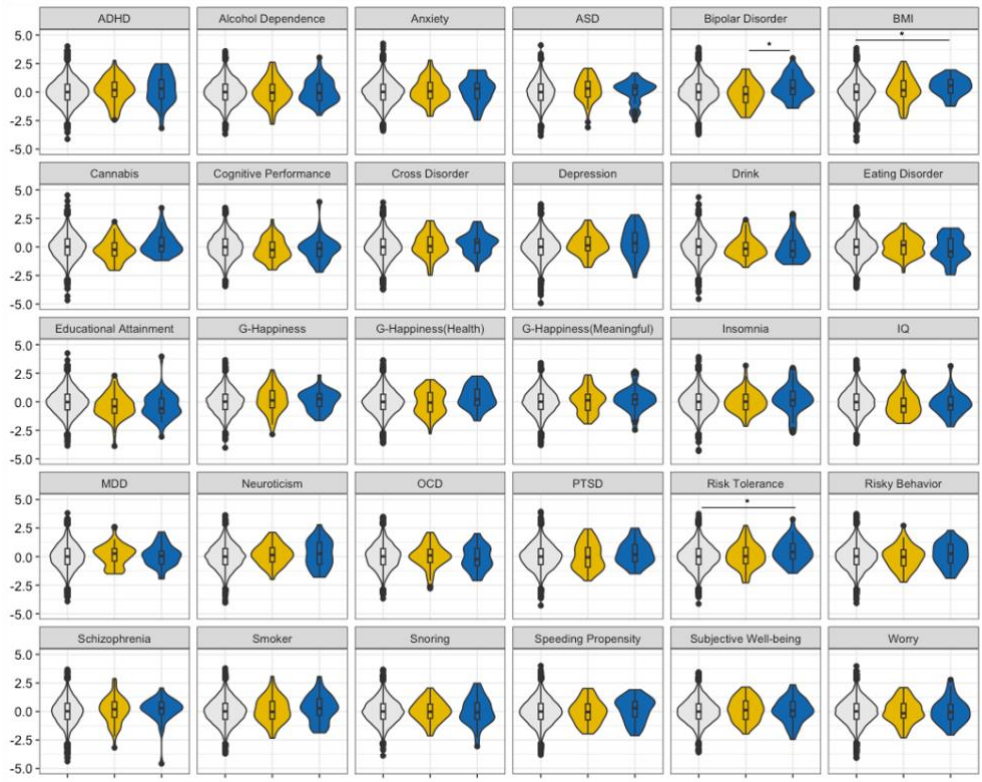

Figure 9. Violin plots of 30 genome-wide polygenic scores and ADHD subgroups with European ancestry only. The non-ADHD group is represented by gray, ADHD-1 by yellow, and ADHD-2 by blue. ASD indicates autism spectrum disorders; BMI, body mass index; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder. **Note,** FDR-corrected post hoc test, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$

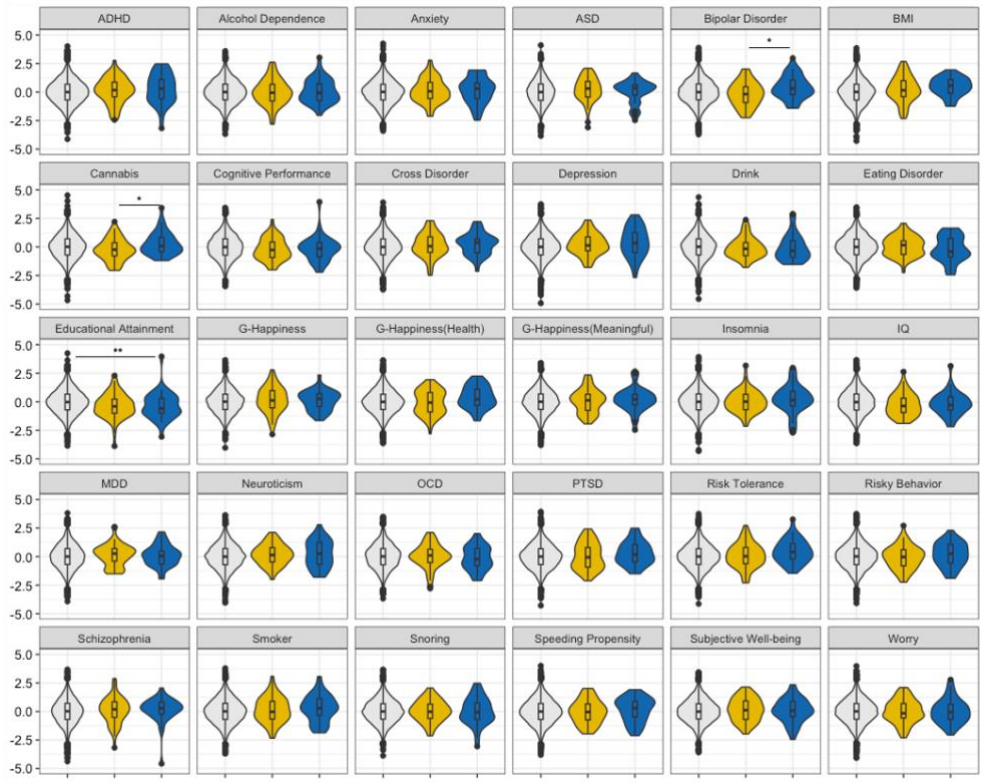

Figure 10 Violin plots of 30 genome-wide polygenic scores and ADHD subgroups with multi-ancestry. The non-ADHD group is represented by gray, ADHD-1 by yellow, and ADHD-2 by blue. ASD indicates autism spectrum disorders; BMI, body mass index; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder. **Note,** FDR-corrected post hoc test, **** $P_{fdr} <$ .0001, *** $P_{fdr} <$ .001, ** $P_{fdr} <$ .01, * $P_{fdr} <$ .05

3.5. Relation to ADHD subgroups and brain measures

In an effort to determine what brain characteristics contribute to the clustering of individuals with ADHD, I analyzed the brain data of 10,152 participants, including non-ADHD (N=9,979), ADHD-1 (N=111), and ADHD-2 (N=62) subgroups. The results were adjusted for the following factors: age, sex, parental income, parental marital status, research sites, and race/ethnicity.

The results showed that individuals with ADHD-1 had decreased cortical measures compared to non-ADHD individuals (**Figure 11. a**). In particular, this was seen in regions such as the lateral orbital frontal (right, mean difference=-.377, P_{fdr}=.047; left, mean difference=-.252, P_{fdr}=.047), entorhinal (mean difference=-.259, P_{fdr}=.008), inferior temporal (mean difference=-.253, P_{fdr}=.020), lateral occipital (mean difference=-.181, P_{fdr}=.030), and right thalamus proper (mean difference=-.119, P_{fdr}=.033). However, no differences were observed in subcortical volumes. The ADHD-1 brain also showed decreased thickness in the lateral orbital frontal region (mean difference=-.279 P_{fdr}<.0001) and decreased surface area and sulcal depth in both the left and right frontal pole (surface area – right, mean difference=-.309, P_{fdr}=.036, left, mean difference=-.147, P_{fdr}=.048; sulcal depth – right, mean difference=-.238, P_{fdr}=.032, left, mean difference=-.280, P_{fdr}=.006). Decreased FA was also observed in the left striatal inferior frontal cortex (mean difference=-.049, P_{fdr}=.036) and the right superior longitudinal fasciculus (mean difference=-.054, P_{fdr}=.035) (**Figure 12. a**).

Similar to the comparison between ADHD-1 and non-ADHD, the brain volumes of individuals with ADHD-2 were found to be reduced compared to those without ADHD (**Figure 11. b**). Notably, this volume reduction was observed across cortical and subcortical regions, including the left and right pallidum, right putamen, and left thalamus. The affected cortical regions included the cuneus, fusiform, and caudal anterior cingulate. The most significant differences were seen in the subcortical regions of the right caudate (mean difference=-1.389, P_{fdr}=.008), left hippocampus (mean difference=-1.386, P_{fdr}=.023), left and right putamen (left,

mean difference=-1.309, P_{fdr}=.013; right, mean difference= -1.286, P_{fdr}=.021). A decrease in surface area was also found, with the caudal anterior cingulate (left, mean difference=-.428, P_{fdr}=.001; right, mean difference=-.342, P_{fdr}=.002), cuneus (left, mean difference=-.233, P_{fdr}=.002; right, mean difference=-.265, P_{fdr}<.0001), fusiform (left, mean difference=-.309, P_{fdr}<.0001; right, mean difference=-.265, P_{fdr}<.0001), and insula (left, mean difference=-.366, P_{fdr}<.0001; right, mean difference=-.375, P_{fdr}<.0001) showing decreases. In terms of white matter tracts, both the left fornix increased in FA (mean difference=.074, P_{fdr}=.049) and MD (mean difference=.307, P_{fdr}=.005) (**Figure 12. b**).

In comparing ADHD-1 and ADHD-2 (**Figure 11. c**), ADHD-2 showed reduced brain volume in the left fusiform (mean difference=-.140, P_{fdr}=.003) and rostral anterior cingulate regions (mean difference=-.440, P_{fdr}=.034). Moreover, there were reductions in the right caudate (mean difference=-1.982, P_{fdr}=.016), left hippocampus (mean difference=-2.056, P_{fdr}=.015), and left putamen (mean difference=-1.790, P_{fdr}=.041) in ADHD-2. On the other hand, the entorhinal (left, mean difference=.517, P_{fdr}=.019; right, mean difference=.355, P_{fdr}=.011) and lateral orbitofrontal cortices (mean difference=.658, P_{fdr}=.006) were thicker in ADHD-2. Regarding white matter tracts, ADHD-2 had decreased right superior longitudinal fasciculus FA (mean difference=-.060, P_{fdr}=.037), while the left fornix MD (mean difference=.034, P_{fdr}=.019) was increased than in ADHD-1 (**Figure 12. c**).

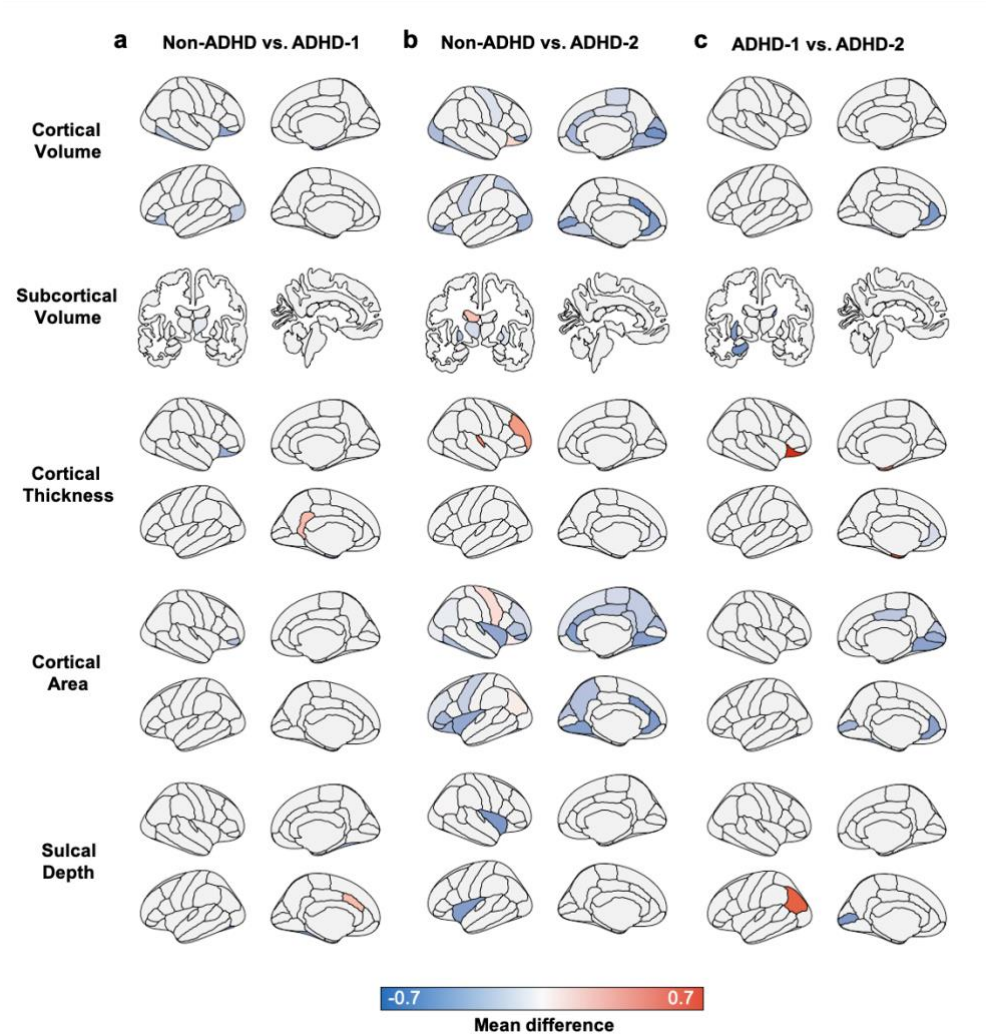

Figure 11. Differences in structural MRI features across ADHD subgroups. a, ADHD-1 and non-ADHD group comparison. **b**, ADHD-2 and non-ADHD group comparison. **c**, ADHD-1 and ADHD-2 comparison. **Note,** The color represents the mean difference between groups, with a range from -0.7 to 0.7. FDR-corrected post hoc test, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$. n.s. indicates non-significant differences.

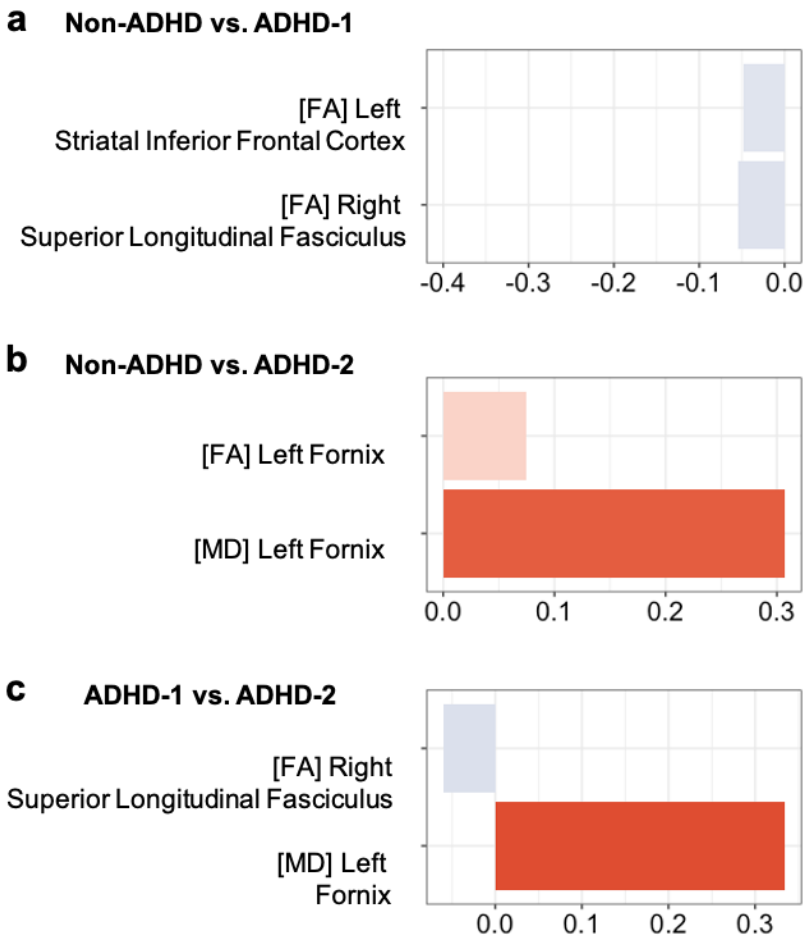

Figure 12. Differences in white matter tracts across ADHD subgroups.

3.6. Developmental changes of each ADHD subgroup

I sought to explore whether the two subgroups of ADHD exhibited different brain developmental changes and trajectories. To this end, I examined the brain developmental changes using delta values (the difference between the 2-year follow-up and baseline data).

For the non-ADHD and ADHD-1 group comparison (**Figure 13. a**), ADHD-1 showed a reduction in volume in cortical regions such as pars opercularis (mean difference=-.221, P_{fdr}=.035) and postcentral (mean difference=-.310, P_{fdr}=.026), and subcortical regions including the lateral ventricles (mean difference=-.437, P_{fdr}=.019) and cerebellum cortex (mean difference=-.365, P_{fdr}=.006). Additionally, there was decreased sulcal depth in the rostral middle frontal (mean difference=-.279, P_{fdr}=.030), lingual (mean difference=-.671, P_{fdr}<.0001), isthmus cingulate (mean difference=-.624, P_{fdr}=.032), and surface area in the precuneus (mean difference=-.347, P_{fdr}=.032), pars opercularis (mean difference=-.208, P_{fdr}=.039), and paracentral regions (mean difference=-.294, P_{fdr}=.033), with the only increased sulcal depth in the left peri-calcarine region (mean difference=.316, P_{fdr}=.017). No significant cortical thickness difference was found between non-ADHD and ADHD-1 groups.

For the non-ADHD and ADHD-2 group comparison (**Figure 13. b**), no significant brain developmental changes were found in both cortical and subcortical volumes. In regards to cortical thickness, the pars triangularis (mean difference=-.373, P_{fdr}=.007) and supramarginal regions (mean difference=-.159, P_{fdr}=.016) were thinner, but the pars orbitalis (mean difference=.389, P_{fdr}=.021) was thicker than the baseline in ADHD-2. There was decreased sulcal depth in the inferior parietal (mean difference=-.516, P_{fdr}=.009), inferior temporal (mean difference=-.659, P_{fdr}=.002), superior parietal (mean difference=-.417, P_{fdr}=.014), and precentral (mean difference=-.425, P_{fdr}=.029) regions, and an increase in the

pars opercularis (mean difference=.404, P_{fdr}=.016) and superior frontal (mean difference=.393, P_{fdr}=.045) regions. A decrease in the right striatal inferior frontal cortex (FA) (mean difference=-.221, P_{fdr}=.041) and left fornix (MD) (mean difference=-.723, P_{fdr}=.027) in the ADHD-2 group, compared to non-ADHD (**Figure 14. b**).

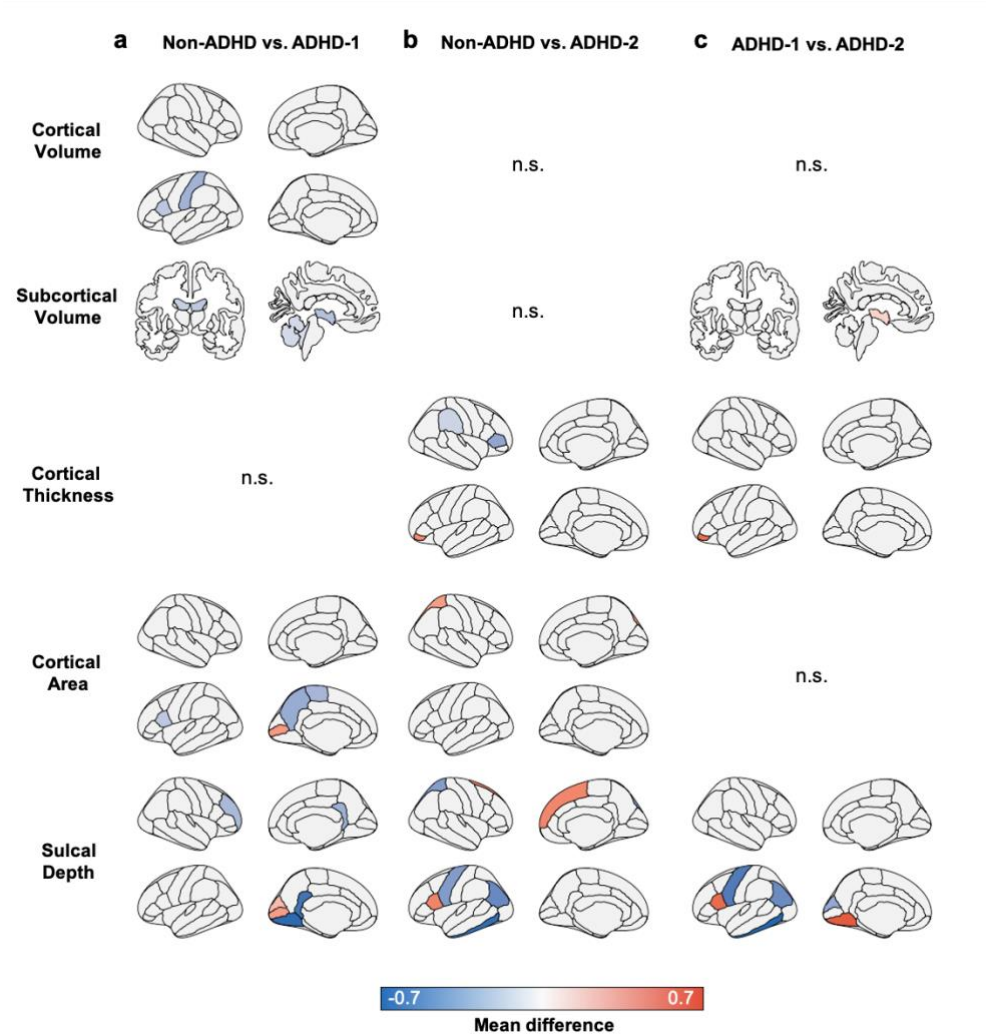

Figure 13. Differences in the developmental change of brain structures across ADHD subgroups. a, ADHD-1 and non-ADHD group comparison. **b**, ADHD-2 and non-ADHD group comparison. **c**, ADHD-1 and ADHD-2 comparison. **Note,** The color represents the mean difference between groups, with a range from -0.7 to 0.7. FDR-corrected post hoc test, **** $P_{fdr} < .0001$, *** $P_{fdr} < .001$, ** $P_{fdr} < .01$, * $P_{fdr} < .05$. n.s. indicates non-significant differences.

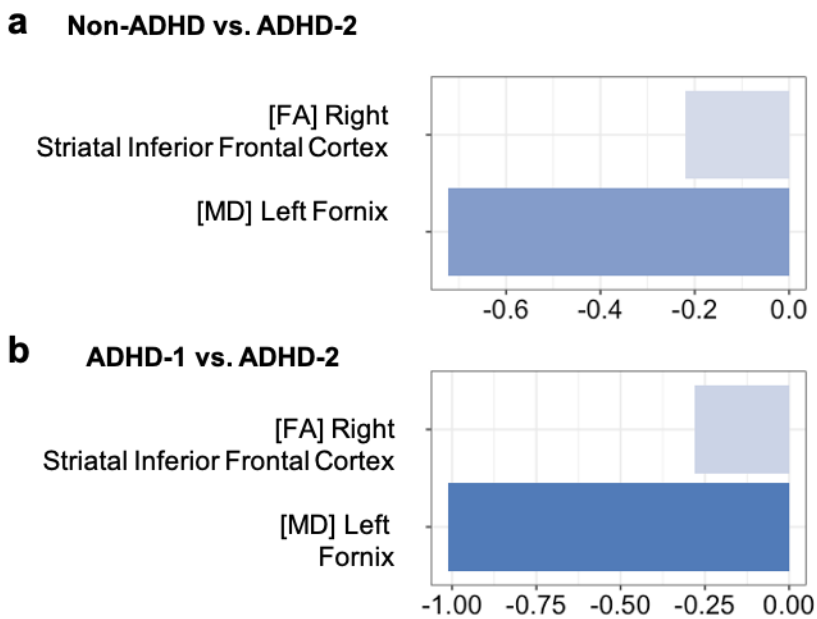

Figure 14. Differences in the developmental change of white matter tracts across ADHD subgroups.

4. CONCLUSION

4.1. Summary

ADHD is a complex neurodevelopmental disorder with multifactorial inheritance. Its heterogeneity has posed a challenge in terms of achieving an objective diagnosis and providing appropriate treatment. This study aimed to examine the heterogeneity of the brain structure in ADHD by using clustering modeling in prepubertal children from an admixed American population. The clustering model revealed two distinct subgroups of ADHD, ADHD-1 and ADHD-2. Demographic differences were identified across the subgroups, therefore corrected in subsequent analysis. Both ADHD subgroups reported higher levels of total, hyperactivity/impulsivity, and inattention symptoms compared to the non-ADHD group, but no differences were found between ADHD-1 and ADHD-2. Notably, the internalizing mood composite was higher in ADHD-2 compared to both ADHD-1 and non-ADHD. European-filtered genetic data analysis showed that three GPSs (bipolar disorder, BMI, and risk tolerance) were associated with differences across ADHD subgroups. Specifically, ADHD-2 had a higher polygenic score for bipolar disorder than ADHD-1, and also higher scores for BMI and risk tolerance compared to non-ADHD individuals. The multi-ancestry analysis yielded similar results for bipolar disorder GPS and also revealed higher lifetime cannabis use GPS and lower educational attainment GPS in ADHD-2. The brain profiles of each subgroup showed that ADHD-1 had reduced cortical measures compared to non-ADHD, but no subcortical volume reductions. ADHD-2 had overall brain volume reduction and decreased surface area across all brain regions, including subcortical regions. Further analysis of brain developmental changes using the longitudinal dataset revealed differences in both cortical volume and cortical thickness between the ADHD subgroups, with ADHD-1 showing only cortical volume reductions and ADHD-2 showing only cortical thickness changes.

4.2. Implication and perspective

ADHD is characterized by a high degree of heterogeneity, as seen in inconsistent or conflicting findings in the brain and behavior. The literature has established that ADHD is associated with structural abnormalities in the brain (Faraone et al., 2015), such as reduced brain volumes in regions like the prefrontal cortex and basal ganglia (Castellanos et al., 2002; Durston et al., 2004; Frodl & Skokauskas, 2012; Greven et al., 2015; Stoodley & Schmahmann, 2009). However, a more recent study utilizing data from the ABCD study found that although overall brain measurements were small, there was no difference in the subcortical volume (Bernanke et al., 2022). Additionally, the findings regarding abnormalities in white matter tracts have not been consistent in ADHD (Chiang et al., 2016; Connaughton et al., 2022; Silk et al., 2009). These conflicting results suggest that there may be heterogeneity within the disorder (Karalunas et al., 2014; Karalunas & Nigg, 2020; Nigg et al., 2020), which recent studies have attempted to explore through dimensional subtyping approaches. This dimensional approach provides a more in-depth understanding of individual variability within the disorder and offers a potential alternative to the traditional approach of comparing ADHD and control groups.

Following these efforts, using supervised clustering modeling, this study presents two distinct subgroups within preadolescent ADHD, each with its own unique GPSs, neuroanatomical characteristics, and behavioral phenotypes. In particular, ADHD-2 showed higher levels of internalizing mood symptoms, genetic scores for bipolar disorder compared to ADHD-1, and BMI and risk tolerance compared to non-ADHD. This is consistent with previous research indicating a close relationship and shared genetic basis between ADHD and bipolar disorder (Demontis et al., 2019). Specifically, bipolar disorder is a mood disorder characterized by episodes of depression, interspersed with mania or hypomania (American Psychiatric Association & Association, 2013). Although ADHD is a neuropsychiatric disorder in childhood and bipolar disorder is commonly

diagnosed in adulthood, both disorders are highly correlated and share a genetic basis. Notably, the manic phase of bipolar disorder is associated with irritability, impulsivity, and intense feelings (Klassen et al., 2010). Furthermore, depression co-occurs with ADHD, which is a key element of bipolar disorder (van Hulzen et al., 2017). Therefore, a higher bipolar disorder GPS in the ADHD-2 subgroup is likely to be associated with heightened internal mood symptoms at a behavioral level. Higher BMI and risk tolerance in ADHD-2 also align with previous findings. In particular, a study has established that there is a correlation between impulsivity symptoms and BMI, as well as between GPS for ADHD and (Barker et al., 2021).

Another pattern to note is that only the ADHD-2 subgroup showed a decrease in brain volume in areas of the basal ganglia such as the pallidum, putamen, and thalamus, not in the ADHD-1 subgroup. Specifically, a reduction in brain volume in these regions can potentially affect normal functioning, leading to difficulties in the regulation of movement and emotional behavior in the pallidum, and problems with motor control, attention, and sensory processing in the putamen and thalamus (Ellison-Wright et al., 2008; Norman et al., 2016; Valera et al., 2007). This finding mirrors the overall decreased volumes of subcortical regions observed in the ADHD-2 subgroup, which is also in agreement with the brain abnormalities seen in ADHD and bipolar disorder (Frodl & Skokauskas, 2012; Rimol et al., 2010; Stoodley & Schmahmann, 2009). This study discovered that ADHD-2 had an increased FA and MD in the left fornix, a white matter tract that carries fibers connecting the hippocampus and hypothalamus, which may contribute to cognitive or behavioral problems (Davenport et al., 2010; Onnink et al., 2015). This finding seems contradictory with earlier reports that individuals with ADHD have abnormally lower FA in the fornix. In contrast, the findings in white matter tracts, which were initially different from previous studies, aligned with prior research's findings when brain developmental change over a two-year period was examined. In ADHD-2, lower MD in fornix and FA in the striatal inferior frontal cortex were observed. These results indicate that brain abnormalities, particularly in the white matter tract, may become evident at a later stage.

Additionally, the analysis of brain development over time using the longitudinal data showed variations in cortical volume and thickness between the ADHD subgroups. This suggests that the trajectory of brain development in ADHD is different from the control group, and this difference also occurs within the ADHD subgroups. Specifically, ADHD-1 decreased both in cortical and subcortical regions, with a reduction in brain volume. Despite the fact that the decrease in subcortical volume is not predominantly located in the basal ganglia, a commonly recognized region in ADHD brain development, the results indicate that this group has abnormal brain volume. Given that gray matter volume and surface area peak during preadolescence, the reduction in brain volume and surface area in the ADHD-1 group may have lasting negative effects. On the other hand, ADHD-2 showed only changes in cortical thickness, indicating a unique pattern of brain development compared to ADHD-1. These results highlight the importance of further investigating brain development in ADHD subgroups. Given the limited understanding of brain development during this stage, it is essential to continue exploring the nuances of these changes and their effects on mental health and cognitive development. Further research is necessary to gain a deeper understanding of the underlying mechanisms and potential protective factors, which can aid in developing more effective interventions to support healthy brain development in preadolescents.

4.3. Limitations and future research direction

The current study provides valuable insights into studying the heterogeneity in ADHD brain based on the large-scale preadolescence population. However, it is essential to consider the limitations that still exist when interpreting the result.

First, our results depend on using multiple imputations to fill in more than half of the teacher's ratings on ADHD. Due to the requirement to consider the DSM-5 diagnostic criteria, teacher's rating scores were included. However, there was a high level of missingness in these scores, necessitating the use of multiple

imputations. While an advanced multiple imputation method (Enders, 2010, 2017; Little et al., 2014; McCartney & Burchinal, 2006; Schafer & Graham, 2002; Van Buuren, 2018) was used to address this issue, and the results were validated through the examination of data distribution, there is still a possibility that the imputation may have limited the study's power.

Another limitation of this study is that the results do not take into account the propensity weighting scores, which correct for sampling bias. Although the ABCD study was designed to collect data from a nationwide population (Casey et al., 2018), further analysis that incorporates covariate controls and propensity weighting methods calibrated to the American Community Survey (ACS) could be employed to account for potential demographic and socio-economic selection bias in the national sample recruitment of eligible children (Heeringa & Berglund, 2020). Additionally, the prevalence of ADHD diagnosis in this study (2.057%) was lower than the known ADHD prevalence (5.3%, CI: 5.01-5.56%) (Faraone et al., 2015), which may be due to the sample bias, so future research should address this issue by correcting the sampling bias.

A third constraint of this study is that the GPSs used to describe the relationship between genes and brain and behavior may not fully reflect all genetic influences. Although there have been recent developments in understanding the genetic roots of ADHD, the modest impact of each genetic factor and the overlap with other mental and physical characteristics make it difficult to establish a causal genetic relationship firmly. Previous studies, for instance, have indicated that the common genetic risk for ADHD contributes not just to ADHD but also to disorders such as depression (Consortium, 2013), conduct problems (Hamshere, Langley, et al., 2013), and schizophrenia (Hamshere, Stergiakouli, et al., 2013).

To further improve the understanding of the heterogeneity of ADHD brain, future studies should address the limitations of the current study. This can be done by using alternative methods to fill in missing data in the teacher's ratings.

Furthermore, larger sample sizes should be used in future studies to increase the power of the results and provide a better representation of the population. In addition, future research should employ propensity weighting methods to control for sampling bias. This can be done by incorporating covariate controls and propensity weighting methods calibrated to the American Community Survey (ACS) or similar sources to ensure a more representative population sample. This will also help address the lower-than-expected ADHD prevalence, as it will allow for a more accurate representation of the general population. Lastly, future studies should further examine the interplay between genetic, environmental, and brain factors that contribute to the development of ADHD. It is important to note that ADHD is influenced by both genetic and environmental factors, and their interaction. Environmental factors like poverty, maternal deprivation, and exposure to toxicants can significantly impact non-inherited familial factors and interact with genetic elements, like DNA variants, to regulate gene expression (Faraone et al., 2015). By considering the complex interactions between these factors, a more comprehensive understanding of the underlying mechanisms that drive ADHD could be established. Additionally, future studies can also consider the relationship between ADHD and other related disorders, such as depression and conduct problems, to better understand the shared genetic risk factors associated with ADHD.

4.4. Conclusion

In conclusion, this study identified two distinct subgroups of ADHD, and each with its own unique features at the genetic, behavioral, and brain levels. The findings suggest the potential for varying brain pathologies within ADHD and the importance of further research to improve diagnostic approaches with the subtyping approach. Investigating the heterogeneity in ADHD would enhance understanding of an individual's unique and shared characteristics across the genetic, brain, and behavioral levels, providing new insights into the disorder.

CONTRIBUTION

Bogyeom Kim, BA, of Seoul National University, Eunji Lee, BA, of Seoul National University, and Yoonjung Yoonie Joo, Ph.D., of Korea University, contributed to processing genotype data and jointly constructing genome polygenic scores (GPSs).

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국문초록

주의력 결핍/과잉행동 장애 (ADHD)는 아동기 가장 흔한 신경 발달 장애 중 하나로, 주의력 결핍, 충동, 과잉 행동을 특징으로 한다. ADHD 뇌에서의 구조적, 기능적 이상성은 대조군과 비교하여 발견되어 왔다. 그러나 이러한 접근은 ADHD 내에서의 개인 변동성과 이질성을 반영하는데 어려움이 있다. 이를 해결하기 위해 본 연구에서는 감독되지 않은 클러스터링 모델을 사용하여 ADHD 뇌에서의 이질성을 분리하고, 분리된 하위 그룹이 서로 다른 임상적 특성과 관련되는지를 조사하고자 했다. 연구 결과, 클러스터링 모델은 두 개의 ADHD 하위 그룹을 밝혀냈다. 두 개의 ADHD 하위 그룹은 대조군과 비교하여 높은 ADHD 증상 수준을 보였지만, 양극성 장애, BMI, 위험 감수의 유전 점수와 내재화 기분 증상에 대해서는 ADHD-2 하위 그룹에서만 유의미한 높은 점수를 보였다. 각 하위 그룹의 뇌 프로파일에서는, ADHD-1 은 일부 영역에서만 피질 측정치가 감소한 반면, ADHD-2 는 전반적인 뇌 부피 및 표면적의 감소를 보였다. 종단 연구 결과에서는 ADHD-1 은 피질 및 피질하 부피의 감소, ADHD-2 는 피질 두께의 감소를 주요 특징으로 하는 등 뇌 발달 과정에서의 패턴 차이를 보였다. 종합하면, 본 연구는 ADHD 뇌의 이질성과 하위 집단 간의 임상적 지표 및 뇌에서의 차이를 조명하여, 향후 진단 및 치료 접근법에 대한 통찰력을 제공한다.

주요어: 주의력 결핍/과잉 행동 장애; 이질성; 신경 하위유형; 비지도 학습 기반 클러스터링 모델
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