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Review Article

Attention-deficit hyperactivity disorder associated gene variants and their impact on neuroanatomy

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by complex genetic and neurobiological underpinnings, with heritability estimates suggesting that genetic factors account for up to 75% of the risk. Neuroimaging studies have consistently demonstrated structural and functional alterations in brain regions such as the frontal cortex, striatum, and cingulate areas among affected individuals. This narrative review synthesizes evidence from genome-wide association studies (GWAS), molecular genetic analyses, and neuroimaging research published between 2005 and 2023 to elucidate the associations between ADHD-related genetic variants and neuroanatomical or functional brain changes. Key genes implicated include DRD4, SLC6A3, COMT, CDH13, and ADGRL3, whose polymorphisms—such as the DRD4 7-repeat allele, SLC6A3 9R/10R variants, and COMT Val158Met—have been linked to altered dopaminergic signaling, reduced gray matter volume, cortical thinning, and disrupted connectivity in fronto-striatal and fronto-parietal networks. Subtype-specific neuroimaging findings further reveal that individuals with the combined subtype exhibit decreased pallidum volume and cingulate cortical thinning, whereas those with the Inattentive subtype demonstrate occipital thinning and insular abnormalities. Collectively, these findings reinforce that ADHD is a polygenic disorder with distinct neuroanatomical correlates underlying its phenotypic heterogeneity and variable treatment responses. Despite progress, inconsistencies in methodology, small effect sizes, and limited population diversity constrain current insights, underscoring the need for longitudinal, multimodal research to refine genotype–phenotype mapping and support precision medicine approaches in ADHD.

Keywords: Attention-deficit/hyperactivity disorder, Genetic variants, Neuroimaging, Dopamine pathways, Polygenic risk, Brain structure

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, characterized by symptoms of inattention, hyperactivity, and impulsivity that significantly impair academic, occupational, and social functioning. The global prevalence of ADHD among children and adolescents is estimated to be around 5–7%, with persistence into adulthood observed in up to 60% of cases.

ADHD not only affects the individual but also exerts profound psychosocial and economic burdens on families and communities, influencing education, employment stability, and interpersonal relationships. The etiology of ADHD is multifactorial, with a substantial genetic component supported by heritability estimates approaching 75%, as indicated by twin and family studies.

Although environmental factors such as prenatal exposure to alcohol, hypoxia, and psychosocial stress contribute to symptom manifestation, genetic predisposition plays a predominant role in disease development. Advances in molecular genetics and neuroimaging have facilitated the identification of key gene variants and brain regions implicated in ADHD pathophysiology.

Genome-wide association studies (GWAS) have revealed that ADHD is a polygenic disorder, influenced by numerous common variants of small effect sizes, including those within genes such as DRD4, SLC6A3, COMT, CDH13, and ADGRL3. These genes are primarily involved in dopaminergic signaling, synaptic plasticity, and neurodevelopmental regulation. Functional and structural neuroimaging studies corroborate these genetic findings, consistently showing abnormalities in the prefrontal cortex, striatum, and cingulate gyrus—regions integral to attention control, impulse regulation, and executive function. Moreover, converging evidence from magnetic resonance imaging (MRI) and functional MRI (fMRI) suggests that distinct ADHD subtypes—predominantly inattentive and combined—exhibit unique neuroanatomical signatures. ADHD-Combined is often associated with reduced pallidum and cingulate volumes, whereas ADHD-Inattentive shows cortical thinning in occipital and insular areas. These neurobiological differences may reflect genotype–phenotype correlations, underscoring the importance of integrating genetic data with neuroimaging findings to better understand ADHD heterogeneity.

This review aims to synthesize current evidence on the relationship between ADHD-associated genetic variants and corresponding neuroanatomical alterations. By combining insights from genomic studies, neuroimaging data, and molecular mechanisms, this work seeks to elucidate the biological pathways linking genetic susceptibility to structural and functional brain changes in ADHD, with implications for diagnosis, subtyping, and personalized therapeutic strategies.

IMPACT OF ADHD ON THE INDIVIDUAL LIFE

ADHD is associated with an individual's health and well-being, so it might impact not just the individual but also their family and society. The preschool child's high levels of activity, limited concentration, and impulsiveness are characteristics of a normal preschool child, as this behavior is typical for their age. Thus, a high level of supervision is needed. However, children with ADHD may stand out. Children with ADHD in this age group may face additional challenges on top of hyperactivity and impulsiveness, such as delayed development and poor social skills, which make it difficult to interact with children of their age group. Primary school children with ADHD can be seen differently. Their peers in class start developing the skills and maturity needed to succeed through primary school, including self-control and better concentration. On the other hand, children with ADHD may struggle academically, making it harder for them to keep up with their peers, which can bring down their self-esteem. ADHD in adolescence, as children transition into adolescence, they might exhibit a decrease in hyperactivity, but inattention and impulsiveness remain persistent. Moreover, they develop antisocial behavior, which creates further challenges. In adult life, about 60% of ADHD patients have continued struggles into adulthood, including frequent job changes and dismissals, and choosing specific similar jobs over other types of jobs. They were experiencing difficulties in communicating with colleagues, attending meetings, and completing tasks on time and with an increased risk of inheriting ADHD from children.[1]

In a study conducted among 2326 caregivers of children and adults (mean age: 11.5, 80% male) from 10 European countries, two-thirds of the caregivers were mothers, and 73% were employed. The burdens reported were categorized as work -6% reported quitting their job, 28% had to change their career or alter their working hours, and missed an average of 3.9 hours per week. Social life, 28% reported planning the day around their children, 14% avoided social activities when with their children, and 20% reported worrying about people's perceptions. Family, a significant strain in the relationship with the partner (16%) and other children (11%) was reported. Stress, approximately 29% reported spending significant time worrying or stressing about their child. Overall, the most commonly reported burden was missing or altering work hours, while the most severe was quitting work.[2]

ADHD symptoms manifest in different forms according to the age of the patient and gender, and there is a significant difference between female and male symptoms, where usually boys show external symptoms such as hyperactivity and impulsivity whereas girls show Internal symptoms such as inattentiveness and low self-esteem, also ADHD is more prevalent in boys more than girls and onset of symptoms are usually in early childhood.[3]

GENETIC BASES OF ADHD

Many theories have emerged to explain ADHD pathophysiology, including the hypothalamic-pituitary-adrenal axis, prenatal ischemia, and prenatal alcohol exposure (PAE). Genetic studies have shown that ADHD is a highly heritable disease, where a systematic review concluded that ADHD has an average of 75% heritability.[4] Genetic factors play a major role in the pathogenesis of ADHD, and further understanding of the underlying genomic architecture can provide important insights into the neurobiology of the disorder. Recent genome-wide association studies have identified several genomic loci associated with ADHD, suggesting that multiple genetic variants with small individual effects influence the disorder.

Table 1 discusses the role of ADHD-associated genes in each of these phases of neurodevelopment.[5]

Studies have shown that ADHD is a highly heritable neurodevelopmental disorder with a substantial genetic component.[5] Recent genetic studies have identified several risk variants associated with ADHD, including both common and rare genetic variants. These findings suggest that ADHD is a polygenic disorder, with multiple genes contributing to its development. The genetics of ADHD are complex, and the precise mechanisms by which genetic factors influence the neurobiology and neuroanatomy of the disorder are not fully understood.[6] Existing research has shown that ADHD-associated genetic variants are enriched in evolutionarily constrained genomic regions and loss-of-function intolerant genes, indicating that they may disrupt critical brain-expressed regulatory processes.[7]

Table 1: The role of ADHD-associated genes in each phase of neurodevelopment.

Gene	Study type	References	Neurodevelopmental process
BDNF	Candidate gene	Hawi et al, Kent et al	Synaptogenesis, selective cell death, glia and microglia
CDH13	GWAS-SNP	Lasky-Su et al	Neurogenesis, connectivity, synaptogenesis
CHRNA7	GWAS-CNV	Williams et al	Synaptogenesis, glia and microglia
DRD5	Candidate gene	Daly et al, Gizer et al	Glia and microglia
FOXP2	GWAS-SNP	Demontis et al	Neurogenesis, migration, synaptogenesis
GIT1	Candidate gene	Won et al	Glia and microglia
GRM1	GWAS-CNV	Elia et al	Neurogenesis, synaptic plasticity, selective cell death
GRM5	GWAS-CNV	Elia et al	Neurogenesis, synaptogenesis, selective cell death
GRM7	GWAS-CNV	Elia et al	Neurogenesis, synaptic plasticity, selective cell death
5-HT1B	Candidate gene	Gizer et al, Hawi et al	Synaptic plasticity
LPHN3/ADRGL3	Candidate gene	Arcos-Burgos et al, Ribases et al	Connectivity, synaptogenesis
MEF2C	GWAS-SNP	Demontis et al	Neurogenesis, synaptogenesis
NOS1	Candidate gene	Reif et al	Neurogenesis, synaptic plasticity, selective cell death, glia and microglia
PARK2	GWAS-CNV	Jarick et al	Neurogenesis, selective cell death
PCDH7	GWAS-SNP	Demontis et al	Connectivity
PTPRF	GWAS-SNP	Demontis et al	Synaptogenesis, selective cell death
SEMA6D	GWAS-SNP	Demontis et al	Connectivity
SLC6A2	GWAS-SNP	Lasky-Su et al	Glia and microglia
SLC6A3	Candidate gene	Cook et al, Gizer et al	Synaptic activity, synaptic plasticity
SLC6A4	Candidate gene	Gizer et al, Manor et al	Neurogenesis, migration, synaptic plasticity, selective cell death
SLC9A9	Candidate gene, GWAS-SNP	de Silva et al, Lasky-Su et al	Synaptic activity
SNAP25	Candidate gene	Brophy et al, Gizer et al	Synaptic activity, selective cell death
SORCS3	GWAS-SNP	Demontis et al	Synaptic plasticity
ST3GAL3	GWAS-SNP	Demontis et al	Synaptogenesis, glia and microglia

A GWAS is an experimental design used to identify genetic variants, particularly single-nucleotide polymorphisms (SNPs), that are associated with specific traits or diseases in populations. It involves scanning the genomes of many individuals to find common genetic markers that correlate with traits of interest, such as diseases or other phenotypic characteristics. GWAS aims to improve the understanding of the genetic basis of complex traits, diseases, and their underlying biological mechanisms, which can lead to advancements in disease prevention, diagnosis, and personalized treatments. GWAS usually requires large sample sizes to detect associations for traits influenced by multiple genetic factors with small effect sizes.[8]

The etiology of ADHD is derived from an assortment of multiple genetic effects on phenotypic outcome, one way to describe the architecture of ADHD. Unlike in Mendelian disorders, where one mutation determines the pathology, in ADHD, susceptibility arises mostly through an additive effect of multiple single-nucleotide polymorphisms (SNPs) spread throughout the genome. With genome-wide association studies (GWAS), the common understanding is that there are many risk loci for ADHD. Still, each variant here contributes only a small fraction to the heritability of the disorder, with polygenic scores (Pgs) accounting for only about 3.6% to 4.0% of the variance in ADHD symptoms. This badly illustrates the complex genetic background of ADHD, an interplay further manipulated by gene-gene interaction and, very importantly, rare variants and structural genomic alterations, along with the all-important gene-environment interaction. At the same time, ADHD is genetically correlated with several other neuropsychiatric and cognitive traits like impulsivity, educational attainment, and other comorbid psychiatric disorders, thus emphasizing the idea that its genetics stretch well beyond core symptoms into many different dimensions of the neurodevelopmental spectrum. Despite advances in polygenic modeling, the clinical utility of Pgs thus remains limited owing to small effect sizes and the multifactorial nature of the disorder itself, with the considerable need for future studies integrating bioinformatics, neuroimaging genetics, and functional genomics to refine risk prediction and the biological mechanisms involved.[9] Additionally, studies have found that ADHD genetic risk is associated with structural and functional differences in brain regions involved in attention, impulsivity, and hyperactivity.[10] A recent GWAS with meta-analysis of ADHD that involves 38,691 who have been diagnosed with ADHD and 186,843 for control the study identified 27 genome-wide significance and 76 potential risks of genes that are many related to early brain development those findings highlight ADHD complex, genetic architecture that involves both common and rare variants and that study they also found that ADHD shares a significant genetic overlap with other psychiatric disorder, like autism and that indicates a common genetic risk factor.[11]

The key genes that show association with ADHD include the following: DRD4, SLC6A3, COMT, CDH13, and ADGRL3. Several genome-wide association studies have been done and highlighted the role of rare copy number variants and genes encoding glutamate receptors. Several studies regarding the neuroanatomy of the brain in ADHD patients show reduced overall brain gray matter volume of about 3-5%, especially in subcortical structures like the caudate and putamen, and also show delayed cortical maturation. Functional MRI studies showed altered activation in frontostriatal, parietal, and attentional networks during cognitive tasks. Also, the genotype-phenotype correlations demonstrate that specific genetic variants, such as the DRD4 7-repeat allele and SLC6A3 haplotypes, are associated with volume changes in some regions in the brain, like the frontal cortex and striatum. Regardless of that, the relationship between genes, environment, and brain anatomy and function in ADHD is still not fully understood and needs further research.[12]

DRD4, the human dopamine receptor 4, is located close to the telomere of chromosome 11p, is responsible for dopamine signaling in the brain, and is involved in attention, motivation, and reward processing, showing a high level of polymorphism expression. It has a polymorphism of a 48-bp variable number tandem repeat (VNTR) in the third exon. The most common reps are 2R,4R, and 7R. The 7R repeats show a lower affinity to dopamine compared to 2R and 4R, which results in disrupting dopamine signaling in the brain, particularly in the frontal cortex and the striatum, affecting attention and motivation shows an association with behavioral traits of ADHD according to in vitro studies that have been done.[13.14]

The SLC6A3 gene encodes the dopamine transporter (DAT), which is the primary protein responsible for the clearance of dopamine from the synaptic cleft in the striatum in the brain.[15] The gene has variable number tandem repeat (VNTR) polymorphism in the 3' untranslated region (UTR); the 9R and 10R are the most common repeats of the gene that have been associated with ADHD. The 9R associated with increased activity of DAT results in a high rate of dopamine reuptake in the brain, resulting in decreased levels of dopamine in the synaptic cleft, particularly in the prefrontal cortex and striatum, which are responsible for attention and impulse control. On the other hand, the 10R allele shows lower DAT activity, leading to prolonged dopamine signaling that may result in enhancing cognitive function. The studies show that individuals with 9R have a higher risk of developing ADHD, while those with 10R show a more protective effect.[16]

The COMT gene encodes the catechol-O-methyltransferase enzyme, which is crucial for the inactivation of catecholaminergic neurotransmitters, including dopamine, particularly in the prefrontal cortex, where dopamine transporters are sparse. One of the gene's notable polymorphisms is the Val158Met variant, which significantly affects enzyme activity. The Val (G) variant has higher enzymatic activity, leading to faster dopamine degradation, while the Met (A) variant is associated with slower dopamine breakdown. This polymorphism has been linked to various neuropsychiatric conditions, including ADHD, where altered dopamine levels may influence symptoms of inattention and impulsivity.[17]

The CDH13 gene encodes the protein cadherin-13, a cell-adhesion molecule involved in neural development, including axonal outgrowth and synapse formation. It has been implicated in several neuropsychiatric disorders, such as ADHD, autism spectrum disorders, and major depression. One notable polymorphism, rs2199430, located in intron 2 of CDH13, affects gene expression levels. GG allele carriers exhibit increased CDH13 expression, which has been linked to altered neural processing during working memory tasks and lower scores in personality traits such as agreeableness. Although not significantly associated with ADHD on a categorical diagnosis level, rs2199430 influences neural and behavioral phenotypes that may contribute to ADHD symptomatology.[18]

The role of the ADGRL3 gene in the development of ADHD remains controversial. While some studies provide strong evidence linking specific ADGRL3 variants, such as rs2345039, to ADHD, particularly persistent combined-type ADHD, other studies fail to replicate these findings.[18,20] This divergence highlights the complexity of

ADHD's genetic basis and suggests that ADGRL3's influence may vary across populations and environmental contexts. Further research with diverse cohorts and refined phenotyping is necessary to clarify the gene's role. Table 2 summarizes ADHD-associated genes and brain regions.

Table 2: ADHD-associated genes and brain regions.

Gene	Function	Key polymorphism(s)	Implicated brain regions	Effects on ADHD
DRD4	Dopamine receptor	48-bp VNTR (7R, 4R)	The prefrontal cortex, striatum	7R → reduced dopamine signaling, linked to inattention/impulsivity
SLC6A3 (DAT1)	Dopamine transporter	3' UTR VNTR (9R, 10R)	Striatum, prefrontal cortex	9R → increased DAT activity, lower dopamine; 10R → protective effect
COMT	Dopamine degradation	Val158Met (rs4680)	Prefrontal cortex	Val (G) → faster dopamine breakdown, cognitive deficits
CDH13	Neural development	rs2199430 (GG allele)	Prefrontal cortex	Altered neural processing, personality traits
ADGRL3	Synaptic signalling	rs2345039	Variable	Mixed evidence for ADHD risk

GENETIC IMPACT ON NEURODEVELOPMENT IN ADHD

Both child and adult ADHD are strongly suggested to be inherited, with heritability estimated at around 40%. Twin studies support the idea that the development of the disorder has a genetic basis. Classification studies also show that first-degree relatives of individuals with persistent ADHD are at a higher risk of having the condition. However, pinpointing the exact genes responsible for this heritability has proven difficult. It's believed that identifying intermediate phenotypes—traits that link clinical symptoms with genetic studies—could help speed up the discovery of related DNA markers. In task-based research, children with ADHD and their unaffected siblings showed reduced activity in the dorsolateral prefrontal cortex and inferior parietal regions during tasks requiring inhibition, when compared to control participants. Interestingly, these findings stood out despite the lack of major performance differences between groups. Structurally, earlier studies found reduced gray and white matter in the left occipital lobe, and smaller brain volume in the right prefrontal area in both ADHD patients and their unaffected siblings compared to controls. However, the ADHD group also showed smaller cerebellar volume than both their siblings and the control group, which implies that while gray and white matter differences may be inherited, cerebellar volume changes might be more directly linked to the disorder itself.

A recent study by Pironti and colleagues explored anatomical intermediate phenotypes in adult ADHD. Both individuals with ADHD and their first-degree relatives showed reduced volume in the right inferior frontal gyrus and increased white matter volume in the posterior region of the right inferior fronto-occipital fasciculus, compared to controls. In addition, both ADHD patients and their unaffected relatives performed worse than controls in sustained attention tasks. Ensuring these results are reproducible remains key as this promising area of genetic and neuroanatomical research continues to grow.[21]

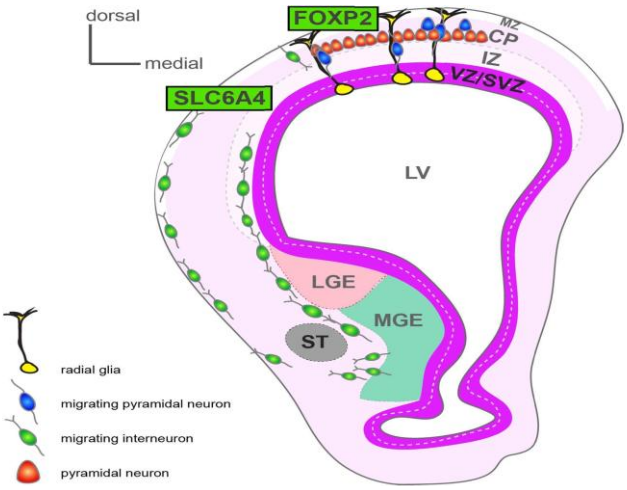

Figure 1: Neurogenesis in the human embryonic neocortex. Coronal section through a human embryonic brain at 12 weeks post conception illustrating newly born pyramidal neurons (blue), generated locally, migrating radially along glial processes, through preceding generations of neurons (red) and settling over them.

Inhibitory interneurons (green) are born ectopically, in subcortical regions and migrate tangentially, forming a deep and a superficial stream to avoid the striatum (ST), which secretes repulsive signals. The interneurons later switch to a radial migratory mode to reach the appropriate cortical layer. ADHD associated genes (boxed) involved in neurotransmitter regulation, participate in the both radial and tangential neuronal migration. CP cortical plate; IZ intermediate zone; LGE lateral ganglionic eminence; LV lateral ventricle; MGE medial ganglionic eminence; MZ marginal zone; ST striatum; VZ/SVZ ventricular/ subventricular zones.[5]

NEUROIMAGING STUDIES ON ADHD

Functional MRI (fMRI) is a neuroimaging technique that measures changes in blood oxygenation and flow in the brain, which are used as indirect indicators of neural activity.[22] fMRI has become a powerful tool for studying the neural underpinnings of ADHD.[22,23]

The purpose of using fMRI to study ADHD is to identify abnormalities in brain structure and function that may contribute to the core symptoms of the disorder, such as inattention, hyperactivity, and impulsivity.[24]

Many studies have suggested that fMRI can differentiate patients with ADHD from healthy individuals. The two most common subtypes of ADHD are predominantly inattentive ADHD (ADHD-I) and ADHD with the combined presentation of both inattention and hyperactivity (ADHD-C).

Figure 2 demonstrates distributed patterns of atypical connectivity compared to typically developing children (TDC), as measured by node strength.[25] Also, the largest study to date of ADHD and cortical surface area and thickness in clinical samples and a pediatric population sample. Reported measuring the cortical thickness in ADHD children and found that there is a decreased thickness in 4 areas, and they are (the fusiform, parahippocampal, and precentral gyri and the temporal pole) as shown in Figure 3.[26]

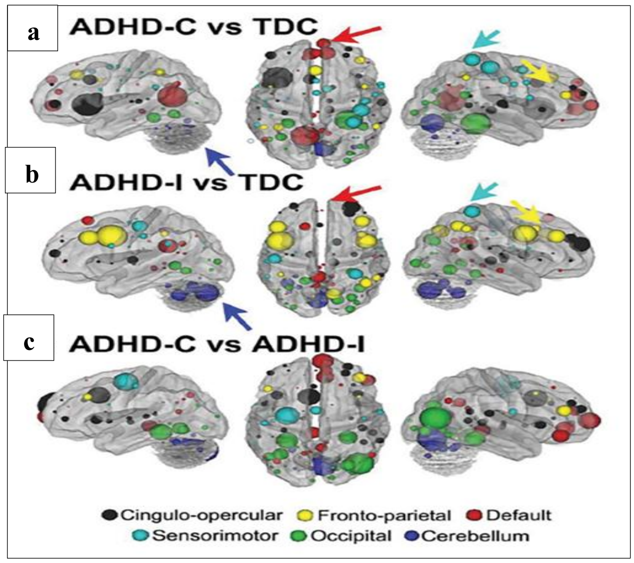

Figure 2: The two most prevalent subtypes of ADHD—predominantly inattentive ADHD (ADHD-I) and ADHD with a combined presentation of both inattention and hyperactivity (ADHD-C)—exhibit widespread patterns of atypical neural connectivity when compared to typically developing children (TDC), as assessed by node strength. The arrows' colors correspond to the anatomical regions represented by the circles in the key.

(a) Node strength comparisons between ADHD-C and TDC reveal marked differences, particularly in the medial prefrontal cortex and other distributed systems; (b) node strength analysis of ADHD-I versus TDC also demonstrates widespread differentiation, with significant nodes in bilateral dorsolateral prefrontal and cerebellar regions, among others and (c) comparisons between the ADHD-C and ADHD-I subtypes highlight similar connectivity patterns. The node colors indicate their respective network classifications.[25]

This study showed that the most consistent finding in ADHD is reduced frontal lobe volume, gyrification, and surface area.[25] However, one of the largest meta-analyses of 96 structural and functional studies on children and adolescents with ADHD found no significant convergence of structural and functional regional alterations, which may be attributable to clinical heterogeneity.[28]

In panel A, Cohen's d effect sizes are shown, with 95% confidence intervals, for case-control differences in ENIGMA-ADHD cortical and subcortical structural features stratified by three age groups: children up to age 14, adolescents from age 15 to 21, and adults older than age 21. Structural features of all regions listed on the x-axis showed significant case-control differences in children; in analyses of cortical and subcortical features, no significant effects were seen in adolescents or adults. This is reflected in the effect sizes shown, all of which reached case-control statistical significance for children but not for the adolescent and adult groups, except for the hippocampus, which shows a significant case-control difference in the adolescent group as well. Panel B shows the heat maps of validated case-control differences in the childhood subset for both surface area and thickness in each hemisphere (Figure 3).[26]

A study consisted of 41 ADHD participants (28 men and 13 women) versus the control group during the performance of the N-BACK test. Red/yellow indicates a positive association (activation) with the task. Blue/green indicates areas where the task decreased the BOLD response (deactivation). The right side of each image represents the left side of the brain. This study showed a failure to deactivate in the medial frontal cortex, an area that forms part of DMN, in adult ADHD patients during the performance of a working memory task.[27]

STRUCTURAL BRAIN CHANGES IN ADHD

Cortical changes

Structural studies consistently reveal cortical thinning in ADHD, particularly in the frontal, temporal, and parietal regions, which are essential for attention and executive function regulation.[31] In ADHD-combined (ADHD-C), these reductions are localized to areas such as the caudal anterior and posterior cingulate cortex, while ADHD-inattentive (ADHD-I) patients exhibit thinning in regions like the lateral occipital and posterior cingulate cortex. Additionally, cortical surface area reductions are observed, with ADHD-C showing decreased areas in the entorhinal and isthmus cingulate regions, and ADHD-I demonstrating reductions in the pars opercularis and insula. The cortical volume follows a similar pattern, with ADHD-C exhibiting lower volumes in the entorhinal and pars opercularis regions, while ADHD-I shows decreased volumes in the caudal middle frontal gyrus.[31] These cortical abnormalities are thought to contribute to the characteristic attentional and executive function deficits seen in ADHD (Table 3 and Figure 4).

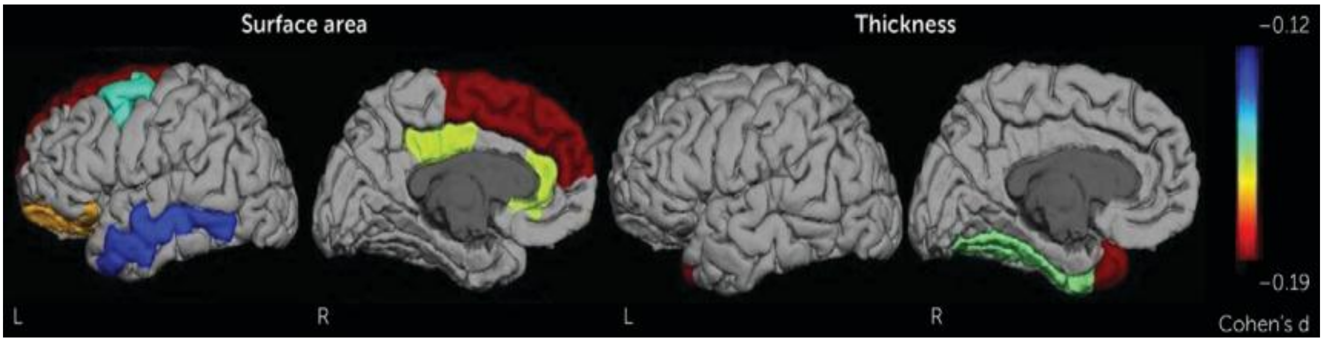

Figure 3: Regional differences in cortical surface area and thickness between children with ADHD and typically developing controls. Colors represent Cohen's d effect sizes (scale: –0.12 to –0.19), indicating regions with significant reductions in surface area (left) and cortical thickness (right) in the ADHD group, L=left hemisphere; R=right hemisphere.[9]

Table 3: Clinical characteristics of the groups.

Characteristics	Mean±SD			F	P		
	Typically developing	ADHD-combined	ADHD-inattentive		1 versus 2	1 versus 3	2 versus 3
ADHD index	29.40±6.49	55.39±7.21	47.72±7.54	265.25	<0.001	<0.001	<0.001
Inattentive	15.82±3.99	28.94±3.67	27.52±4.24	247.47	<0.001	<0.001	0.298
Hyper/impulsive	13.58±3.68	26.44±5.07	20.37±6.11	120.40	<0.001	<0.001	<0.001
Full4 IQ	118.07±13.28	110.29±13.06	103.43±12.86	27.28	0.004	<0.001	0.036
Verbal IQ	120.45±13.45	115.95±16.73	108.20±14.72	15.48	0.264	<0.001	0.029
Performance IQ	111.38±14.36	101.47±13.65	97.07±13.67	24.32	<0.001	<0.001	0.393

1: Typically developing group, 2: ADHD-combined group, and 3: ADHD-inattentive group

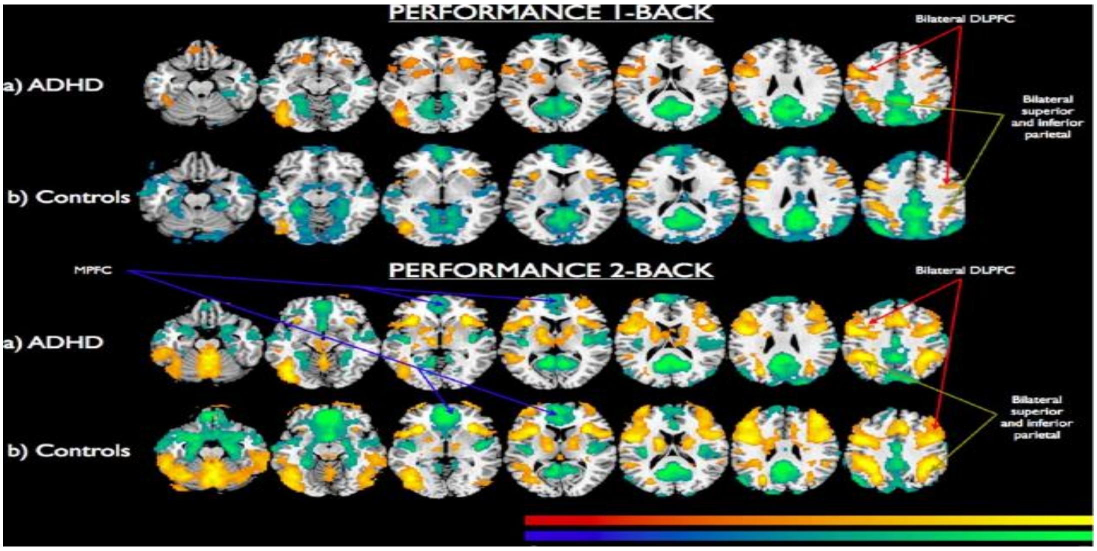

Figure 4: Brain activation during the N-BACK task in adults with ADHD (n=41) versus controls. Red/yellow indicate activation, blue/green indicate deactivation. ADHD participants showed reduced deactivation of the medial frontal cortex, part of the default mode network (DMN).

A meta-analysis highlighted the decrease in gray matter volume compared to controls in the right basal ganglia, anterior and posterior insular cortex, ventromedial orbitofrontal cortex, medial prefrontal cortex, rostral anterior cingulate cortex, and left occipital lobe (Figure 5).[30]

Figure 5a shows results of VBM meta-analysis for, from top to bottom, patients with ADHD relative to controls, patients with obsessive-compulsive disorder (OCD) relative to controls, the comparison between ADHD (versus controls) and OCD (versus controls), and conjunction/disjunction analysis of ADHD and OCD abnormalities (versus controls). The vmOFC GMV deficit is shared between disorders, while the insula/putamen GMV deficit is dissociated between disorders, that is, larger in OCD and smaller in ADHD. Figure 5b shows results of fMRI meta-analysis for, from top to bottom, patients with ADHD relative to controls, patients with OCD relative to controls, and the comparison between OCD (versus controls) and ADHD (versus controls). Figure 5c shows multimodal fMRI-VBM conjunction/ disjunction analysis for, from top to bottom, overlapping deficits in patients with ADHD relative to controls, overlapping deficits in patients with OCD relative to controls, and the comparison between patients with OCD (versus controls) and patients with ADHD (versus controls). Green indicates an increase in patients with OCD versus controls. Warm colors (yellow in ADHD, red in OCD) indicate a decrease in patients versus controls. Orange indicates shared decreases in patients relative to controls. Purple indicates regions that were disjunctive across modalities (i.e., increased in one but decreased in the other) in ADHD compared with OCD (versus controls).[30]

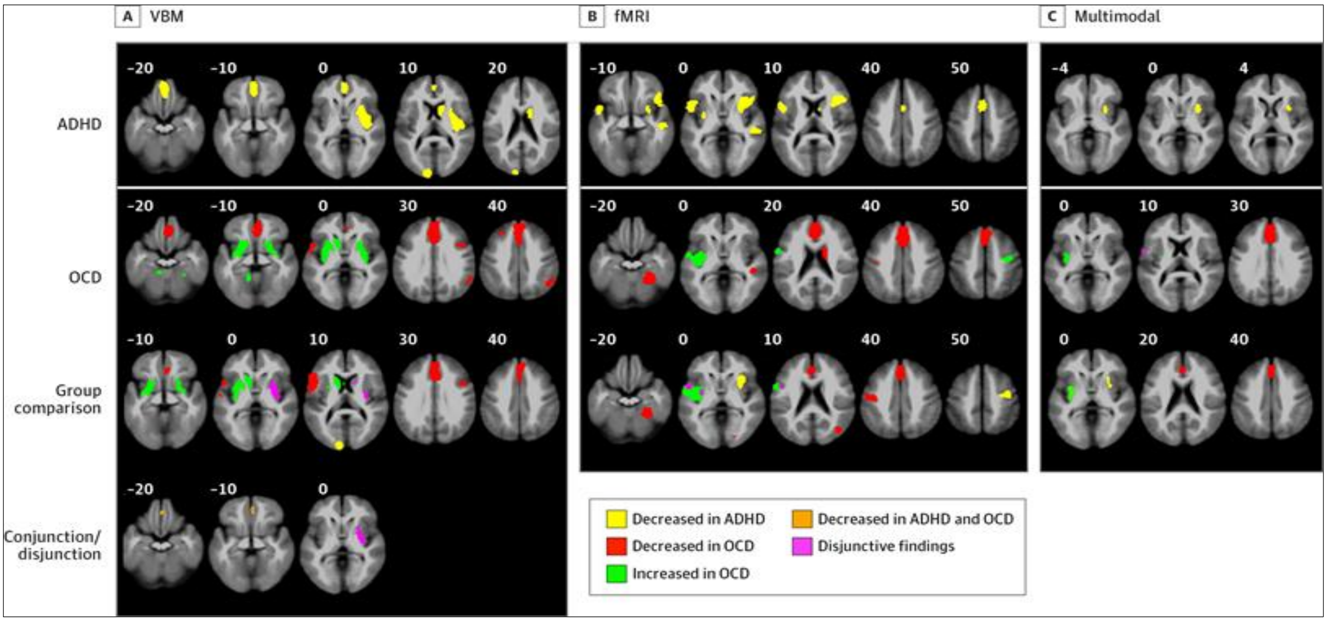

Figure 5: VBM meta-analysis.

Table 4: Meta-analysis results for voxel-based morphometry studies in ADHD and OCD.

Contrast	X	Y	Z	SDMz score	P value	Voxels, no.	Brodmann areas
ADHD-decreased versus control							
Right putamen/pallidum/insula	24	-8	7	2.303	<0.001	1550	13
vmOFC/vMPFC/rACC	2	41	-21	2.270	<0.001	1350	11,10,9,32
Right caudate nucleus	18	8	14	2.154	<0.001	370	
Left occipital lobe	-10	-94	14	1.768	<0.001	336	17,18
OCD versus control							
OCD increased versus control							
Left putamen/caudate/nucleus accumbens/pallidum/amygdala/insula	-28	4	2	2.588	<0.001	1482	13
Right putamen/nucleus accumbens/pallidum/amygdala/insula	24	4	-2	2.089	<0.001	928	13
Left cerebellum	-14	-40	-24	1.349	<0.001	196	
Right cerebellum	23	-37	-24	1.224	<0.005	12	
OCD decreased vs control							
r/dACC/MPFC/vmOFC	-2	28	36	2.693	<0.001	3299	32, 24, 8, 9, 10, 11
Left VLPFC/premotor/STL	-52	18	12	2.315	<0.001	997	44, 45, 46, 9, 43, 22
Right angular gyrus	52	−56	38	1.718	<0.001	274	39, 40
Right DLPFC/premotor cortex	42	12	32	1.589	<0.005	80	9, 6
Left DLPFC	-28	34	38	1.610	<0.005	54	9

Continued.

Contrast	X	Y	Z	SDMz score	P value	Voxels, no.	Brodmann areas
ADHD (versus control) versus OCD (versus control)							
ADHD (versus control) decreased versus OCD (versus control)							
Left putamen/caudate nucleus/nucleus accumbens/pallidum/amygdala/insula	-28	4	-2	1.904	<0.001	1333	13
Right putamen/caudate nucleus/nucleus accumbens/pallidum/amygdala/insula	24	4	-2	1.738	<0.001	841	13
Left occipital lobe	-10	-94	12	1.342	<0.001	294	17,18
Right caudate nucleus	14	16	4	1.323	<0.001	65	
vmOFC	-4	56	-26	1.297	<0.001	51	11
OCD (versus control) decreased versus ADHD (versus control)							
r/dACC/MPFC	2	28	28	1.622	<0.001	1425	32, 24, 8, 9
Left VLPFC/STL	-52	14	10	1.383	<0.001	925	44, 45, 9, 22
Right DLPFC/premotor cortex	44	12	32	1.052	<0.001	120	9, 6
vmOFC/vACC	6	32	-10	1.154	<0.001	114	11, 24, 32

dACC=Dorsal anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; dMPFC=dorsomedial prefrontal cortex; MTL=middle temporal lobe; MNI=Montreal Neurological Institute; rACC=rostral anterior cingulate; rMPFC=rostromedial prefrontal cortex; STL=superior temporal lobe; vACC=ventral anterior cingulate cortex; VLPFC=ventrolateral prefrontal cortex; vmOFC,=entromedial orbitofrontal cortex; vmPFC=ventromedial prefrontal cortex.

Subcortical changes

Subcortical changes further distinguish ADHD subtypes, particularly reductions in the pallidum volume, which are significantly pronounced in ADHD-C but minimal in ADHD-I.[29] Studies have also identified reductions in hippocampal subfield volumes, such as the subiculum, in ADHD-C patients, while these regions remain unaffected in ADHD-I. These subcortical structural differences align with the observed clinical symptoms, where hyperactivity and impulsivity are associated with anterior cingulate cortex and pallidum abnormalities, while cognitive deficits are linked to insula changes. These findings emphasize the role of subcortical regions in the heterogeneity of ADHD and their contributions to the disorder's core behavioral and cognitive manifestations.[29] These structural abnormalities correlate with clinical symptoms, such as hyperactivity and impulsivity, which are linked to reductions in the anterior cingulate cortex, and cognitive deficits, which correspond with changes in the insula and pallidum.[29] Despite these consistent findings, variability in structural alterations across studies highlights the complexity of ADHD's neural architecture and the influence of methodological differences, clinical heterogeneity, and sample size on outcomes.

Functional connectivity

Functional connectivity changes in ADHD have been extensively studied, revealing critical insights into the disorder's neurobiological basis. Notably, adolescents with ADHD exhibit disrupted functional connectivity between the right inferior frontal cortex (rIFC) and various brain networks.

fMRI studies show that upregulation of the rIFC through neurofeedback training enhances its connectivity with the dorsal caudate and anterior cingulate cortex—key regions within the cognitive control network—while decreasing its connectivity with posterior default mode network (DMN) regions, such as the posterior cingulate cortex and precuneus.

These changes correlate with clinical improvements, including reduced inattentiveness and hyperactivity, suggesting a relationship between connectivity modulation and symptom alleviation.

The findings highlight the potential for targeted interventions to restore balance within task-positive and task-negative networks, addressing core ADHD deficits.[29]

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DISCUSSION

This review integrates genetic and neuroimaging evidence to elucidate how ADHD-associated gene variants contribute to neuroanatomical alterations underlying the disorder. Consistent with genome-wide association studies, ADHD demonstrates a highly polygenic architecture, with multiple small-effect variants influencing dopamine regulation, synaptic function, and neurodevelopmental pathways.[6,7,11] These findings support the concept that ADHD's genetic predisposition manifests through specific patterns of cortical and subcortical brain changes affecting attention, motivation, and executive function.

The DRD4 gene, particularly the 7-repeat polymorphism, is associated with reduced receptor sensitivity and diminished dopaminergic signaling in the prefrontal cortex and striatum. This aligns with the findings of Ding et al and Van et al who demonstrated that such polymorphisms alter dopamine receptor function and contribute to behavioral phenotypes of inattention and impulsivity.[13,14] Neuroimaging studies have also identified corresponding volume reductions and connectivity abnormalities in these regions, supporting the link between DRD4 variants and fronto-striatal dysregulation in ADHD.[12]

Similarly, the SLC6A3 (DAT1) gene, which regulates dopamine reuptake, has been widely studied for its role in ADHD. The 9R allele has been associated with increased dopamine transporter activity, resulting in lower extracellular dopamine levels in the striatum.[15,16] These biochemical effects correlate with findings of reduced striatal and prefrontal volumes and disrupted connectivity in ADHD patients, indicating that SLC6A3 polymorphisms may alter the structural and functional integrity of attention and reward-processing circuits.[26]

The COMT Val158Met variant modulates dopamine metabolism within the prefrontal cortex. Individuals carrying the Val allele exhibit faster dopamine degradation and lower prefrontal dopamine availability, contributing to executive dysfunction and attentional deficits.[17] These neurochemical effects correspond to neuroimaging results showing cortical thinning and reduced prefrontal activation during cognitive control tasks.[27,28] Together, these findings highlight COMT's role in shaping the cognitive and behavioral characteristics of ADHD through altered fronto-executive circuitry.

The CDH13 gene encodes a cell adhesion molecule critical for synaptic formation and neural development. Polymorphisms such as rs2199430 have been associated with altered neural processing and personality traits related to ADHD symptomatology.[18] These molecular findings correspond with evidence of reduced cortical volume and disrupted connectivity in prefrontal and insular regions, emphasizing the gene's contribution to neurodevelopmental pathways underlying ADHD.[5]

Finally, the ADGRL3 (LPHN3) gene has been linked to combined-type ADHD and symptom persistence across the lifespan. Studies have shown that ADGRL3 variants (e.g., rs2345039) influence synaptic signaling and are associated with abnormal pallidum and cingulate cortical volumes.[19,20,29] These findings support the hypothesis that ADGRL3 contributes to both behavioral control and motor regulation deficits through its effects on fronto-striatal connectivity.

Across neuroimaging modalities, ADHD consistently exhibits cortical thinning in the frontal, parietal, and cingulate cortices, alongside subcortical volume reductions—particularly in the pallidum and hippocampus.[29,30] Such structural changes are subtype-specific, with ADHD-combined showing greater reductions in cingulate and pallidal regions, while ADHD-inattentive is characterized by thinning in the occipital and insular cortices.[29] These findings align with meta-analyses that have reported widespread structural and functional brain differences in ADHD, reflecting its heterogeneous neurobiological profile.[25,28]

In summary, converging genetic and neuroimaging evidence indicates that ADHD arises from complex interactions between gene variants and neurodevelopmental processes. Specific polymorphisms in DRD4, SLC6A3, COMT, CDH13, and ADGRL3 influence dopaminergic transmission and brain morphology in regions critical for attention and behavioral control. These insights enhance our understanding of ADHD's neurobiological underpinnings and highlight the potential for genotype-based subtyping and personalized interventions. However, methodological variability and small effect sizes remain limitations. Future longitudinal studies integrating genomics, imaging, and behavioral data are essential to clarify the causal mechanisms linking genetic variation to neuroanatomical and cognitive outcomes.

CONCLUSION

This review demonstrates that ADHD is a complex neurodevelopmental condition influenced by multiple genetic variants that converge on key neurobiological pathways. Evidence from genome-wide association and neuroimaging studies indicates that variants in genes such as DRD4, SLC6A3, COMT, CDH13, and ADGRL3 affect dopaminergic signaling, synaptic organization, and neurodevelopmental processes, leading to structural and functional alterations in brain regions governing attention, executive function, and behavioral control.

Cortical thinning and subcortical volume reductions, particularly within the prefrontal cortex, striatum, pallidum, and cingulate cortex, are consistent neuroanatomical markers associated with ADHD. These findings suggest that the heterogeneity observed among ADHD subtypes may stem from distinct genetic and neurobiological mechanisms influencing regional brain development.

Understanding the interplay between genetic variants and neuroanatomical changes provides a foundation for future precision medicine approaches, enabling subtype-specific diagnosis and individualized treatment strategies. However, current limitations—including small effect sizes, sample diversity, and methodological inconsistencies—underscore the need for large-scale, longitudinal, and multimodal studies integrating genetic, neuroimaging, cognitive, and environmental data. Such research will be pivotal in clarifying causal pathways and advancing toward a more personalized model of ADHD care.

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