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Review Articles

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ADHD: A Critical Review of Dopamine Genes and Cortical Thickness as Etiological Mechanisms

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ABSTRACT

Literature on the role of the dopaminergic system in attention-deficit/hyperactivity disorder (ADHD) is rich, and more recent studies supporting dopaminergic genetic mechanisms as the basis for ADHD symptomatology continue to make headway. Likewise, the relationship between cortical thickness (CT) and ADHD is well-researched, though exact mechanisms remain unclear. Although the exact etiology remains unclear, the vast field of ADHD research indicates that the disorder's complex etiology and pathophysiology are the likely product of interactions between genetic and environmental factors, resulting in increased susceptibility and neurostructural differences. The relationships between dopamine (DA) and CT and their underpinning genetic mechanisms, i.e., relevant polymorphisms and developmentally driven aspects of gene expression, beg for further exploration. However, the nature of this association remains somewhat undefined as the research is plagued by limitations related to genetic, structural, and functional imaging techniques, inconsistent subtype categorization, and a need for more ethnically- and age-diverse participants. This critical review analyzes the current state of the literature and calls for more research that explores linkages between dopamine genes, CT, and ADHD, with particular consideration of the impact of neurodevelopment across the lifespan.

Keywords: ADHD, Executive Function, Dopamine, Cortical Thickness

Attention-deficit/hyperactivity disorder (ADHD) is associated with a variety of deficits in executive function and neurocognitive ability, including but not limited to difficulties with response inhibition, working memory (WM), emotion regulation, and sustained attention [1]. Although the exact etiology of ADHD remains unknown, ADHD is one of the most prevalent childhood-onset neuropsychiatric disorders [2]. As one of the most prevalent neurodevelopmental disorders in children, ADHD can significantly impact academic, behavioral, and social development and related outcomes [3]. Furthermore, ADHD's most commonly associated symptoms—distractibility, impulsivity, and hyperactivity—present significant and persistent challenges to most individuals well into adulthood, making an improved understanding of the disorder's underlying biological mechanisms all the more critical [2,4].

As a disorder characterized by executive dysfunction in a number of domains, clarification of structural abnormalities associated with cognitive functioning in ADHD populations is critical [3]. Although the exact etiology remains unclear, the vast field of ADHD research indicates that the disorder's complex etiology and pathophysiology are the likely product of interactions between genetic and environmental factors, resulting in increased susceptibility and symptom-amplifying neurostructural differences [1]. More explorations of the pathophysiology of ADHD are needed to clarify the relationships between genetics, brain structure, and behavior in the disorder's etiology [3].

Brain Morphometry and ADHD

Brain structure and volume change dynamically throughout the first ten years of life, with maturation and subsequent synaptic pruning continuing to occur well after this period [5]. Recent studies employing brain morphometry analyses have implicated cortical thickness (CT) as a possible predictor of differences

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in WM and inhibitory control in children and adolescents with ADHD [6]. To further explore the possibility of structural and functional differences in clarifying ADHD's etiology, brain imaging methods such as magnetic resonance imaging (MRI), i.e., structural magnetic resonance imaging (sMRI) and functional magnetic resonance imaging (fMRI), have been employed. MRI findings have suggested structural differences or abnormalities in individuals with ADHD, one being differences in CT, though findings have been inconsistent [7].

Previous research suggests relationships between individual differences in CT and the gray matter volume in brain structures associated with executive function and emotion regulation [5]. However, the nature of this association remains somewhat undefined, with previous studies implicating CT in a broad array of brain structures concerning both internalizing and externalizing problems (i.e., behavioral problems associated with regulatory processes and skills) [5]. Notably, along with volume and surface area, CT reflects brain maturation throughout development, i.e., the lifespan [5]. This process is uniquely relevant in exploring the relationships between CT and executive function, as CT has implications in synaptic creation, dopamine (DA) signaling, and pruning [5,6,8].

Critical Review

The present paper aims to critically examine current directions and perspectives in ADHD research, with particular focus given to emerging research employing brain imaging technology to clarify structural and functional differences related to ADHD, executive dysfunction, and relevant neurodevelopmental mechanisms. First, aspects of executive function that are commonly implicated in ADHD symptomatology are explored in relation to developmental differences in brain morphology (i.e., CT). Findings that explore ADHD symptomatology and aspects of executive dysfunction in clinical and healthy populations are included. Next, ongoing theories examining the role of dopamine (DA) and DA-related genes in terms of their influence on brain morphology and symptom severity are reviewed. The present paper highlights two facets of the current ADHD etiology literature, i.e., dopaminergic genetic and developmental mechanisms, in an effort to illustrate remaining deficits in understanding and current barriers to replicability and call for research that unifies both perspectives and clarifies their dynamic relationship in the etiology and neurobiology of ADHD.

Developmental Implications in Executive Functioning and ADHD Symptomatology

Si et al. explored the relationship between regional cortical morphology abnormalities and WM deficits in individuals with ADHD [3]. The study employed a small sample size (N = 36). Moreover, DSM-IV diagnostic criteria were utilized in determining ADHD group eligibility [3]. Notably, the results revealed cortical morphology abnormalities in children with ADHD, i.e., differences in CT in the bilateral frontal and temporal cortices, compared to healthy controls [3]. However, it should be highlighted that results revealed some inconsistencies regarding CT as an indicator of significant differences between ADHD populations and healthy controls [3]. Differences in CT were only indicated prior to correction for multiple comparisons. That said, the findings discussed by Si et al. further suggest and support previous research findings indicating a relationship between the structural and functional (e.g., WM) differences observed in the ADHD population [3].

More research is needed to clarify the mechanisms that underpin and influence this relationship [3]. Additionally, previous research has associated ADHD with proposed delays in cortical maturation, noting sMRI findings of prefrontal and precentral region cortical thinning [3]. Regarding theories related to maturational differences in children with ADHD, Si et al. found that children with ADHD appeared to lag in cortical thickness as compared to healthy controls—but, once again, more research is needed to clarify the mechanisms that influence this relationship [3]. Notably, study limitations included the small sample size (N = 72; 36 participants diagnosed with ADHD and 36 healthy controls), which limited analyses related to differences across ADHD subtypes, and the inclusion of participants with comorbid learning disorder and disruptive behavior disorder diagnoses—understudied and potentially confounding influences on cortical morphology.

Ewell and colleagues explored the relationships between CT, emotion regulation, and emotional reactivity in an early to mid-childhood, non-clinical population. Additionally, Ewell et al. considered the developmental processes associated with changes in CT [5]. As discussed, individuals with ADHD often experience deficits in WM and have difficulty with response inhibition and emotion regulation, three facets of executive function [5,6]. Previous research indicates that neural structures like the prefrontal and cingulate cortices—and more specifically, the inferior frontal gyrus (located within the PFC)—play a role in self-regulatory aspects of executive functioning [5]. Noted changes in CT occur throughout maturation and support many aspects of executive functioning skills, including self-regulation [5]. Ewell and colleagues found that greater CT in the insula, especially the thickness of the insula in the right hemisphere, was associated with emotion regulation [5]. Conversely, reduced CT in the inferior frontal gyrus was associated with emotional reactivity, especially in the right hemisphere [5]. Notably, study outcomes support previous research implicating areas of the frontal cortex and temporal lobe in emotion regulation and emotional reactivity [5].

Ewell et al. focused on effects during early and mid-childhood, only including children ages 3 to 8 [5]. Crucially, current literature indicates that CT may decrease linearly over time, i.e., from early childhood to adolescence. Therefore, longitudinal studies examining the impact of potentially dynamic maturational changes on CT and related aspects of emotional functioning are critical to further understanding [5]. Notably, the relationships between CT, emotional reactivity, and emotional regulation revealed in the Ewell et al. study were somewhat limited by the predominantly white, middle-class participant group [5]. Future research exploring the relationship between cortical morphology and various aspects of executive functioning, like emotional reactivity and regulation, should include more ethnically and socioeconomically diverse samples [5].

In their 2023 study, Ewell and colleagues utilized sMRI due to the nature of the relatively young study sample (i.e., ages 3 to 8) for whom fMRI may have presented more challenges (i.e.,

movement or fidgeting concerns). Though understandable, the differences in sMRI and fMRI regarding neural information output must be acknowledged. While interdependent, structure and function present distinct findings. Future replications of the Ewell et al. study should include additional fMRI to flesh out the potential mechanisms underlying CT and regulation or reactivity further [5]. Lastly, the researchers utilized the Emotion Regulation Checklist (ERC) completed via parent report to obtain measures of participant emotion regulation and reactivity (e.g., emotional self-awareness, negative affect, emotional lability, dysregulation) [5]. However, parental reports via the ERC may be subject to social desirability effects or item effects (i.e., the responses to various items of the ERC may more accurately measure other aspects of emotional functioning outside of regulation or reactivity) [5]. Future studies should combine checklists or behavior rating scales with behavioral observations, including play-based frustration or inhibitory control tasks [5].

Previous research has indicated the presence of an age-dependent cortical thinning process in the ADHD population (as well as in other neuro-atypical populations) [7]. Boedhoe and colleagues compared morphological brain abnormalities across populations with traits related to impulse control deficits (i.e., deficits in such executive functioning skills as response inhibition and cognitive control). Using imaging techniques, the researchers explored structural brain differences across ADHD, autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD). In a large sample (N = 12,198), the researchers explored the similarities and differences in various aspects of brain morphometry, including CT, across clinical and healthy controls [9]. Structural MRI (sMRI) results suggested similarities in children (i.e., participants younger than 12 years of age) with ADHD and ASD in CT, as opposed to control subjects [9]. However, these differences did not appear significant in the adolescent group (age 12 and below) [9]. The researchers theorized that the differences in CT, i.e., thinner frontal and temporal cortices, found in the ADHD and ASD population may indicate generally delayed brain development [9]. Notably, the linkages between CT in frontal regions and executive dysfunction found in previous studies were not supported by imaging results of the ADHD population in this study [9]. That said, variations across scanners and protocols used in different studies certainly limit outcome clarity and future replicability [9].

Research findings have varied regarding which brain regions in the ADHD population demonstrate the most significant variability in CT compared to "typical" controls [7]. Levman and colleagues explored the relationship between regional CT and ADHD symptom presentation in a large (N > 600) youth sample (ages 7 to 21) [7]. The researchers were especially interested in the potentially predictive abilities of CT in differentiating diagnostic likelihood across subtypes of ADHD (i.e., the inattentive vs. combined subtypes), and they found that variations in CT across brain regions appeared to differ significantly across ADHD presentation-type—inattentive, hyperactive, or combined [7].

Significant differences in mean CT across several cortical regions in the ADHD cohort were revealed [7]. Across all age groupings (i.e., ages 5-10, 10-15, and 15-20), Levman et al. found the greatest CT variability differences in the caudal middle frontal region, superior frontal gyrus, and middle frontal gyrus [7]. Interestingly, Levman et al. also found greater variability in the mean CT of the younger (age 0 to 5) ADHD population—specifically, in the right angular and left supramarginal gyrus—which was not indicated in older age groups [7]. However, it should be noted that differences in CT variability in the ADHD group were reported across the lifespan (i.e., this study employed participants ranging from 0 to 21), which signifies the critical role of neurodevelopment in cognitive functioning [7]. Theories about this phenomenon implicate neural fibre tract development and pruning, speculating that individuals with ADHD may experience reduced or delayed pruning [7].

Levman et al.'s findings support previous research indicating ADHD type-specific differences in CT as well as the presence of age-related or developmental mechanisms. Levman and colleagues theorized that neuronal pruning leads to decreases in CT and that the varying CT revealed in the ADHD population might imply developmental differences or delays [7]. Notable study limitations for consideration included a lack of data regarding participant symptom severity or pharmacological treatment exposure in the ADHD group and questionable reliability regarding Free Surfer (an automatic segmentation program) analyses of imaging results in participants aged 0-to-8 months.

DA Signaling as the Driver of CT and ADHD

Given ADHD's symptomatology as a disorder of executive function, a deeper exploration of the DA-implicated cortico-striatal and fronto-parietal networks that modulate impulsivity, motivation, and cognitive control, is essential to improving etiological understanding and developing more effective intervention measures [8]. Previous research implicates the dopaminergic system and its dysfunction in the pathogenesis of ADHD [10]. Notably, previous researchers have explored the impact and associations of genetic variations, i.e., polymorphisms, across various dopamine (DA) transporters (i.e., DAT) and receptors (e.g., the DA D5 receptor gene, DRD5; the DA D2 receptor gene, DRD2; and the DA D4 receptor gene, DRD4), their associated signaling processes, and their role in ADHD symptom presentation [10].

Fernández-Jaén and colleagues explored the role of the cingulate cortex (CC) in the pathophysiology of ADHD [8]. Notably, the cingulate cortex is implicated in the DA system and is involved in the dopaminergic neurotransmission processes performed by the dopamine transporter gene (DAT1)—one of the best-replicated ADHD candidate genes [8]. Research implicates DAT1 in the neural activity of various cortical regions and the striatum, indicating variations in activation and regulation within the cortico-striatal-thalamo-cortical pathway [8]. Understanding the role of cortical thickness in ADHD symptom presentation and underlying genetic associations may yield improved ADHD treatment as the most common current psychopharmacological interventions aim to increase DA availability in the synapse [8]. Examinations of the relationship between CT and DA function as a product of associated genetic polymorphisms and a producer of executive function (or dysfunction) are underrepresented in the literature.

Fernández-Jaén et al. examined this relationship via a childhood (ages 6 to 17) ADHD patient sample [8]. In their 2018 study, Fernández-Jaén et al. assessed ADHD symptom severity via the Conners-3 ADHD rating scale, grouped participants by genotype (i.e., patients with the 10-Repeat DAT1 allele and those without), and obtained measures of cognitive functioning (i.e., FSIQ), medication-status, and DSM diagnostic status. The researchers found that structural differences in the CC—specifically, greater CT in the right cingulate gyrus—were associated with the DAT1 gene variation in the ADHD patients studied [8]. The study findings highlight the need for future explorations of the relationships between genetics, brain structure, and behavior and support previous research indicating the unique role of the CC in terms of ADHD symptom presentation [8]. However, study findings should be considered with regard to limitations. First, the ages of the ADHD patient sample ranged from childhood to adolescence, potentially confounding study results due to the impact of age and development on gene expression. Also, the researchers only included a clinical sample; however, the inclusion of health controls in a future study would allow for analyses related to the effect of DAT1 on CT in non-clinical and sub-diagnostic populations. Additionally, participants with comorbid learning disability, oppositional defiant disorder, anxiety, and depression were included in the study.

It is important to note that genes "shape" brain morphometry [11]. That said, brain structure undergoes dynamic changes across the lifespan, with changes linked to shifts in cognitive performance over time [11]. The genes that influence the dopaminergic system and DA function appear to have a relationship with cognitive aging.

More specifically, the genes associated with DA signaling greatly impact cognitive performance and, possibly, influence the changes in brain structure associated with aging [11].

Miranda and colleagues theorized that the changes in CT that occur in the heteromodal association cortices influence cognitive performance via their role in the dopaminergic system [11]. Their 2021 study examined the DRD2 (i.e., a dopamine receptor) single-nucleotide polymorphism (SNP), one of the genes that influence the DA D2 receptor system, in relation to its influence on cognitive function and brain structure during the aging process [11]. DA D2 receptors are expressed throughout the cortex and striatum and are particularly concentrated in the prefrontal cortex [11]. However, DA signaling and binding potential changes with age and appear to explain decreases in various cognitive performance aspects observed in aging populations [11].

Miranda et al. theorized that genetic polymorphisms like DRD2 C957T demonstrate the potential impact of genotype influence across the lifespan, with DRD2 C957T impacting D2 receptor availability and binding potential and having an increasing effect on cognitive performance with age [11]. Notably, the researchers identified various aspects of brain structure potentially impacted by the DRD2 polymorphism, including cortical thickness and, in turn, potentially influencing D2 availability in the striatum [11].

The study took place in an adult population (ages 20 to 94). It examined the influence of DRD2-related reductions in CT on cognitive performance, specifically on executive function tasks like cognitive switching, flexibility, and inhibition (measured via the Stroop color word interference task and the Wisconsin Card Sorting Task) [11]. Results indicated significant decreases in CT across the lifespan and, notably, the DRD2 polymorphism was a significant predictor of CT and was significantly associated with deficits in executive function performance [11]. Miranda et al. found that thinner mesocortical tissue was the underlying driver of the poor executive function performance of DRD2 polymorphism carriers [11]. Study results clarified the potential influence of genotypic differences, especially those that impact D2 availability on CT and, in turn, impact executive function [11]. However, it should be noted that age-related effects of DRD2 were not found [11].

Conclusion: Next Steps

A deeper understanding of the etiological mechanisms that influence ADHD will require significant efforts aimed at explaining linkages between DA, CT, and development. Crucially, the relationships between DA and CT and their underpinning genetic mechanisms, i.e., relevant polymorphisms and developmentally driven aspects of gene expression, beg for further exploration. To effectively draw these connections, future research must include larger sample sizes, ethnically diverse participants, clinical and healthy controls, task-based measures; genetic, structural, and functional imaging techniques; and a dimensional, rather than categorical, view of ADHD (in order to reflect sub-diagnostic levels of dysfunction that have relevance to potentially negative outcomes). The successful dissemination of future research clarifying the relationships between ADHD symptom presentation and severity, DA genes, and associated morphological differences, i.e., CT variability, will enable better clinical symptom and diagnostic predictions, elucidate potential neurodevelopmental trajectories in terms of executive function, and lead to more effective psychopharmacological interventions.

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