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# The Neurobiology of ADHD



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### **DEFINITION OF TERMS**

Brain networks - Discrete areas of the brain that work together to perform complex tasks Catecholamines - Monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) Coherence - When brain regions have similar neuronal oscillatory activity with each other Copy number variants - Variations in the number

of genes or sections of DNA from one individual to the next

**Epigenetics** - Mechanisms for regulating gene expression that involve postgenomic alterations in DNA and chromatin structure rather than variations in genetic sequence

**Etiopathogenesis** - Classification of a disease/ disorder that is based on its cause/development **Executive function** - Higher-level cognitive processing, including planning, goal-directed behavior, and cognitive flexibility

**Radioligand** - A substance used in research that binds to a targeted receptor for the purpose of sensitive and quantitative detection

**"Top-down" regulation of emotion** - Emotional regulation that is in response to a cognitive appraisal of an event (in comparison to "bottom-up" regulation, which is based on how the event is emotionally perceived)

Bolded terms above correspond to bolded terms in monograph.

### INTRODUCTION AND EPIDEMIOLOGY

Attention deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder.<sup>1,2</sup> The prevalence of ADHD in children and adolescents in the United States and around the world is approximately 9% to 11%, with roughly 4% to 5% continuing to have ADHD as adults.<sup>3-6</sup> ADHD is a childhood-onset developmental disorder with core symptoms of inattentiveness, impulsivity, and/or motor unrest (ie, hyperactivity) that occur to a degree beyond what would be expected based on the child's age, developmental level, and intellectual level.<sup>7</sup> Furthermore, varying degrees of emotional dysregulation, irritability, deficits in executive function, behavioral disturbances related to impulse control (eg, oppositional defiant, conduct disorders), learning disabilities, and motor disturbances (eg, tics), as well as other psychiatric conditions (eg, anxiety, depression), frequently accompany an ADHD diagnosis.8,9

This monograph reviews the neurobiological basis of ADHD, including genetics, brain networks, structural and functional brain changes, and altered neurotransmission.

### DIAGNOSIS AND CONSEQUENCES OF ADHD

Clinical definitions of ADHD have progressed from George Still's "defect in moral control" in 1903 to "hyperkinesis" in the 1930s, to "minimal brain dysfunction" and "hyperactive child syndrome" in the 1950s.<sup>8</sup> In 1980, the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)* has a diagnosis of attention deficit disorder, with or without hyperactivity, and *DSM-IV* and *DSM-5* include 3 ADHD subtypes: predominantly inattentive, predominantly hyperactive/impulsive, and combined.<sup>8,10,11</sup>

ADHD usually does not occur as a single psychopathology; approximately 75% of patients with ADHD have at least 1 comorbid psychiatric condition (eg, depression, anxiety, substance abuse), which can mask underlying ADHD, make differential diagnosis more challenging, and predict a worse prognosis.<sup>7,12</sup> In a longitudinal analysis of a large birth cohort followed through age 18 to 19 years, individuals with ADHD had significantly higher rates of comorbid depression, bipolar disorder, and anxiety disorders compared to individuals without ADHD.<sup>13</sup> By adulthood, up to 50% of individuals with ADHD have developed depression, with up to 35% suffering from anxiety.<sup>14</sup> Is this a consequence of ongoing distress due to suboptimal ADHD treatment or a consequence of ongoing changes in the neural circuitry of ADHD which is shared with mood and anxiety disorders?<sup>15</sup> Further research is needed before this question can be answered.

The importance of effective, evidence-based ADHD treatment should not be underestimated, especially as the impact of the disorder can be pervasive and lifelong.<sup>16</sup> Consequences of ADHD include increased risk of school failure and injuries in children and adolescents, and car accidents (fatal and nonfatal), substance use/abuse/dependence, unplanned pregnancy, sexually transmitted diseases, criminal behavior, employment/financial issues, and relationship problems/divorce in adolescents and adults.<sup>3,13,17-23</sup> ADHD also imparts a higher mortality rate. Studies show up to a 3-times greater risk of premature death and up to a 4-times greater risk of death from all causes in individuals with ADHD compared to individuals without ADHD, often due to accidents and trauma, comorbid psychiatric disorders, and suicide.<sup>24-27</sup> Importantly, pharmacotherapy has been found to significantly reduce the risk of many of these consequences, including repeating a grade, motor vehicle accidents, trauma leading to emergency room visits, and criminality, as well as improve quality of life and social/family functioning.<sup>28-34</sup> ADHD treatment has also demonstrated a reduced risk of developing common psychiatric comorbid conditions, as well as reducing their risk of recurrence.<sup>34-37</sup>

### **GENETICS AND EPIGENETICS OF ADHD**

ADHD is one of the most heritable psychiatric disorders, with heritability estimates ranging from 75% to 90%.<sup>38,39</sup> Although identical twin studies have demonstrated consistently high concordance rates (68%-81%), first-degree relatives have only a modest risk of manifesting ADHD (approximately 20%), consistent with a complex polygenetic pattern of inheritance.<sup>39</sup> There are several sources of relevant information regarding genetic contribution to ADHD, including genomewide association studies (GWAS), research focusing on rare but very influential **copy number variants** (CNVs), studies examining associations between candidate genes and ADHD, and work examining interactions between genes and environment.

Some GWAS research has yielded surprising findings related to ADHD and its shared genetics with other psychiatric disorders, with major depressive disorder the closest genetic "relative" to ADHD.<sup>40</sup> A recent, very large-scale GWAS of approximately 20,000 individuals with ADHD and approximately 35,000 controls found that a genetic makeup that carries a risk of ADHD is also associated with increased risk of mood disorders, including depression, mood swings, anxiety disorders, bipolar disorder, irritability, and addictive behaviors, including alcohol use/dependency (Figure 1).<sup>41</sup> It is anticipated that additional research will clarify whether tendencies toward higher risk for these disorders/behaviors are true comorbidities of ADHD or are manifestations of the ADHD genetic underpinning itself. Other candidate genes that have been implicated in ADHD **etiopathogenesis** include those involved in the neurotransmission of dopamine (DA), norepinephrine (NE), serotonin (5-HT), and glutamate (Glu).<sup>42,43</sup>

Rare (<1% frequency), subtle chromosomal mutations, deletions, and duplications (CNVs) may play a substantial role in contributing to ADHD risk.<sup>9,43,44</sup> In fact, one study found that approximately twice as many individuals with ADHD than without carried large CNVs (15.6% vs 7.5%).<sup>45</sup> CNVs associated with ADHD include genes involved in calcium signaling, glutamatergic transmission, and regulation of sleep-wake behavior and vigilance.<sup>46-48</sup>

Numerous environmental risk factors which interact with genetic and **epigenetic** vulnerabilities play a significant role in the etiology of ADHD.



ADHD, attention deficit/hyperactivity disorder; BMI, body mass index.

These include poor maternal nutrition, maternal anemia, parental psychopathology and lower socioeconomic status, complicated and stressful pregnancy/birth, prematurity, low birth weight and small head circumference, and prenatal exposure to drugs (eg, tobacco, cocaine, alcohol, antidepressants) and toxins (eg, lead).<sup>2,49-51</sup> Furthermore, a number of childhood adversities, such as viral infections (including meningitis/ encephalitis), cerebral trauma, epilepsy, anemia, and disorders of the endocrine, immune, and metabolic systems, have all been implicated as risk factors for ADHD.<sup>49</sup>

In summary, genetic research indicates that ADHD is not due to a single gene.<sup>39</sup> Rather, it appears that a large number of genes with minor effects, CNVs, and interactions between genes and environmental risks/adversities all play a relevant role in the pathogenesis of ADHD.<sup>39,44,49</sup> These studies also offer insight into the association of ADHD and mood dysregulation, anxiety, and substance use, which leads to the question whether these are traits inherent in the expression of ADHD or symptoms of truly comorbid disorders. Future genetic studies may clarify the role of developmental phases in gene-environment interactions, provide a better understanding of the link between genetics and specific neurobiological underpinnings of ADHD subtypes, and provide guidance for the most effective treatment choices.

**KEY TAKEAWAY:** The pathogenesis of ADHD is complex, involving an interplay of genes and environment.

### **STRUCTURAL BRAIN CHANGES**

Dysfunctional brain areas frequently implicated in the pathophysiology of ADHD are the prefrontal cortex (PFC, including the dorsolateral prefrontal cortex [DLPFC] and the ventrolateral prefrontal cortex [VLPFC]), anterior cingulate cortex (ACC), parietal cortex, striatum, and cerebellum (Figure 2; Table 1).<sup>52,53</sup>

Structural imaging studies have found reduced gray matter volume in most of the brain structures implicated in the pathogenesis of ADHD.<sup>2,54,55</sup> Reduced striatal volume is one of the most replicated findings in the brains of individuals with ADHD.<sup>55,56</sup> Imaging studies have also noted reduced volume of the PFC (including the DLPFC) and the ACC (**Figure 3**), corpus callosum, and cerebellum, as well as the globus pallidus, caudate nucleus, and thalamus (**Figure 4**).<sup>57-59</sup> Relevance of structural changes in the pathophysiology of ADHD is

| Structure  | Function  |  |
|--|---|--|
| Prefrontal cortex  | Attention, planning, working memory (DLPFC); behavioral inhibition (VLPC); complex decision making, strategic planning (VMPC)   |  |
| ACC  | Movement (caudal regions); attention, cognition (anterior regions); emotion, motivation<br>(rostral and ventral regions); affective and cognitive components of executive control<br>(dorsal regions) |  |
| Cerebellum   | Motor control; cognitive and affective processes  |  |
| Parietal cortex  | Orientation of attention  |  |
| Basal ganglia (includes the striatum<br>[caudate nucleus, putamen] and<br>globus pallidus) | Motivation, reward processing, goal-directed behavior, motor control  |  |

#### Table 1. Brain Structures Implicated in ADHD and Their Functions<sup>15,52,60-62</sup>

ACC, anterior cingulate cortex; ADHD, attention deficit/hyperactivity disorder; DLPFC, dorsolateral prefrontal cortex; VLPC, ventrolateral prefrontal cortex; VMPC, ventromedial prefrontal cortex.





ADHD, attention deficit/hyperactivity disorder.

## Figure 3. Reduced volume (in blue) in the dorsolateral prefrontal cortex and anterior cingulate gyrus (adapted from Seidman 2006).<sup>58</sup>



CGa, anterior cingulate gyrus; DLPFC, dorsolateral prefrontal cortex.

### Figure 4. Reduced volume (green) in the globus pallidus, caudate, and thalamus. $^{\rm 57}$



supported by studies that have noted a relationship between frontal, temporal, caudate, and cerebellar volumes and ADHD symptom severity.<sup>63</sup> Furthermore, reduced thalamic and ventrostriatal volumes have been found to significantly correlate with measures of impulsivity, hyperactivity, and inattention in individuals with ADHD compared to individuals without ADHD.<sup>64,65</sup> Total brain volume is also reduced, with studies reporting volumes 3% to 5% smaller in individuals with ADHD compared to individuals without ADHD.<sup>62,63</sup>

In addition to decreased brain volume, delayed cortical development is also seen in children with ADHD compared to children without.<sup>66</sup> A landmark study conducted in 2007 found that peak cortical thickness was achieved, on average, 3 years later in children with ADHD relative to controls.<sup>66</sup> The delay was longest in the PFC (approximately 5 years in the middle PFC), an area important for executive functioning, reward, memory, suppression of inappropriate responses, and motor control.<sup>66</sup> Extending these findings, a group of authors reported "normalization" of caudate volume over the course of extended maturation.<sup>63</sup> Sophisticated diffusion tensor imaging studies have discovered delayed/reduced myelination of prefrontal-striatal tracts, cortico-cortical connections, thalamocortical white matter tracts, and connections within the default mode network (DMN; including prefrontal, cingulate, and parietal cortices and temporal lobes) in individuals with ADHD compared with controls.<sup>67-69</sup> These differences may be responsible for the delayed development of cognitive-executive control observed in ADHD.<sup>67-69</sup>

Cortical thinning, like cortical thickening, is a normal brain process.<sup>70</sup> However, enhanced cortical thinning in children and adolescents with ADHD vs controls has been found, with significant differences noted in areas important for attentional and motor output (eg, prefrontal regions).<sup>71</sup> Cortical thinning has also been reported in longitudinal structural studies of adults with ADHD, with the rate of cortical thinning correlating with the number of ADHD symptoms.<sup>72,73</sup> Furthermore, convergence toward normal brain dimensions was only observed in young adults whose symptoms remitted compared with individuals who remained symptomatic.<sup>73</sup>

**KEY TAKEAWAY:** Individuals with ADHD exhibit reductions in gray matter volume, delayed cortical maturation, and enhanced cortical thinning, which have been shown to be related to ADHD symptomatology.

### BRAIN NETWORKS AND FUNCTIONAL BRAIN CHANGES

**Brain networks** involved in attention and, therefore, especially relevant to ADHD, include the cognitive-executive network, the cortico-striatal-thalamic-cortical network, and the cortico-limbic network (Figure 5; Table 2).

The cognitive-executive network (Figure 5A) is composed of interconnected cortical areas that have a role in executive function and working memory and in selective and sustained attention.74,75 Dorsal prefrontal cortical areas participate in "top-down" regulation of emotion.75-77 In addition, prefrontal cortical areas are connected to premotor cortices, where they participate in the planning of motoric activity, with abnormalities in these connections found in individuals with ADHD.<sup>15</sup> The cortico-striatal-thalamic-cortical network (Figure 5B) comprises parallel loops that connect the PFC with the basal ganglia and thalamus.<sup>15,78</sup> The network is relevant in ADHD because it has a role in regulating ascending sensory information that reaches the PFC and assigning salience to this information (ie, selecting what information is important and what is not), as well as in motivation and inhibiting inappropriate actions.<sup>78</sup> Interestingly, diminished activity of this network during tasks of motor inhibition and cognitive shifting have been shown to correlate with persistence and severity of ADHD

### Table 2. Brain Networks Involved in ADHD<sup>1,15,74-76,78-83</sup>

| Network   | Components  | Function  |
|---|---|---|
| Cognitive-executive<br>network                    | DLPFC, posterior parietal cortex  | Involved in executive function, working memory, selective<br>and sustained attention; regulating emotion; planning of<br>motor activity |
| Cortico-limbic network                            | VLPFC, amygdala, hypothalamus, brainstem  | Regulating level of arousal   |
| Cortico-striatal-<br>thalamic-cortical<br>network | PFC, basal ganglia, thalamus  | Regulating and assigning salience to sensory information;<br>inhibiting inappropriate actions, motivation                               |
| Default mode network                              | MPFC, posterior cingulate cortex, lateral parietal cortex, precuneus, medial temporal lobe          | Involved in self-reflection, planning future activities, monitoring environment   |
| Dorsal attentional<br>network                     | Precentral and parietal regions   | Mediating goal-directed, executive control processes,<br>including reorienting attention during visual attentional<br>functioning       |
| Motor network                                     | Primary and secondary motor cortices,<br>supplementary motor area, putamen,<br>thalamus, cerebellum | Involved in motor activity  |
| Ventral attentional<br>network                    | Temporoparietal junction, frontal operculum, anterior insula  | Monitoring environment for emergence of salient stimuli<br>and interrupting ongoing activity when necessary                             |
| Visual network                                    | Occipital visual cortex and temporal structures   | Interacting with dorsal attentional network to maintain attention and suppress attention to irrelevant stimuli                          |

ADHD, attention deficit/hyperactivity disorder; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; PFC, prefrontal cortex; VLPC, ventrolateral prefrontal cortex.





A. Cognitive-executive network





### C. Cortico-limbic network



symptoms.<sup>84,85</sup> Connections in the cortico-limbic network **(Figure 5C)** originate from the ventral PFC and link to limbic areas, such as the amygdala and hypothalamus, as well as with brainstem NE nuclei that regulate level of arousal.<sup>76,81,86</sup> Dysfunction of these connections in ADHD may result in emotional lability and deficits in impulsivity and motivation.<sup>80</sup> More recent understanding of the neurobiological underpinnings of ADHD is based on resting functional network imaging. Altered activity in functional brain networks involved in ADHD is hypothetically linked to compromised response inhibition and impulsivity, difficulty sustaining and appropriately shifting attention, altered arousal and vigilance, deficits in working memory and executive function, and impairment of social cognition.<sup>53-55,87-89</sup> Functional imaging studies have also looked at fronto-amygdalar connections and the ventral attentional network. Atypical fronto-amygdalar connectivity and reduced VLPFC-amygdalar connectivity in ADHD has been linked to inadequate emotional control and emotional reactivity (behaviors that sometimes accompany ADHD),<sup>90</sup> while malfunction of ventral attentional pathways has been associated with motivational deficits and difficulty delaying gratification (common symptoms of ADHD).<sup>2</sup> Moreover, VMPFC functional deficits have been linked not only to impaired motivational control, but also to conduct disorder in individuals with ADHD.<sup>91</sup>

Resting functional network imaging is also used to support more contemporary elaborations of ADHD underpinnings. The frontoparietal network includes the DLPFC, VLPFC, anterior PFC, ACC, and the inferior parietal lobes (these regions are also described as the cognitive executive network [CEN]), as well as the lateral cerebellum, caudate, and anterior insula. Its main role is to exercise executive control and participate in decision making. Most of the components of this network demonstrate reduced activity in individuals with ADHD, except the dorsal ACC, which has demonstrated heightened activity (possibly a compensatory adaptation) in some studies.<sup>1,92,93</sup> The previously mentioned ventral attentional network shares components with the salience network and includes the temporoparietal junction, operculum, and anterior insula. It is tasked with monitoring the environment for emergence of salient stimuli and interrupting ongoing activity

when necessary.<sup>1</sup> The dorsal attentional network is composed of precentral and parietal regions (also shares components with the CEN) and appears to have diminished activity in ADHD, which coincides with inattentiveness, working memory deficits, and inadequate response inhibition.<sup>1</sup>

The motor network includes the primary motor cortex, secondary motor cortex (ie, the premotor cortex and supplementary motor area), primary and secondary sensory cortices, putamen, thalamus, and cerebellum.<sup>1,94</sup> Individuals with ADHD have been shown to manifest decreased activation of the primary and premotor cortices compared with controls. Substantially reduced cortical inhibition in ADHD has been correlated with deficient motor performance.<sup>1</sup>

The visual network includes the occipital visual cortex and temporal structures. It interacts with the dorsal attentional network to maintain attention and suppress attention to irrelevant stimuli.<sup>1</sup> Decreased cortical and gray matter volume in the occipital cortex has been reported in individuals with ADHD.<sup>1,95</sup> Interestingly, a 33-year follow-up study of childhood-diagnosed ADHD found an association between persistence of an ADHD and decreased occipital cortical thickness.<sup>1</sup>

Main hubs of the DMN are the medial prefrontal cortices, posterior cingulate cortex, precuneus, and medial temporal lobe.<sup>1,82</sup> Increased DMN activity coincides with self-reflection, rumination, reminiscing, processing social information, and planning future activities.<sup>96</sup> Typically, the DMN is not active when an individual is engaged in cognitive-executive tasks.<sup>96</sup> Convergent imaging evidence suggests that individuals with ADHD have diminished recruitment of DMN activity when engaged in tasks requiring focus and sustained attention.<sup>97</sup> Daydreaming and distractibility commonly described in children with ADHD may be a consequence of inadequate DMN suppression during cognitive tasks.<sup>1</sup> Proper

deactivation of DMN in ADHD occurs only in circumstances of elevated salience or with stimulant use.<sup>1,98</sup> One can wonder whether the tendency to procrastinate in individuals with ADHD may be a pseudo-adaptive maneuver directed toward increasing salience and suppressing distracting DMN activity. Further supporting these findings, newer studies have found decreased connectivity between the dorsal and ventral attentional networks and increased connectivity within the DMN in individuals with ADHD relative to controls.<sup>99,100</sup>

Due to the high rate of comorbid depression and anxiety in ADHD,<sup>7</sup> one may question whether these 3 disorders share common neurobiological alterations. A recently published paper looking at mood and anxiety disorders evaluated whether their shared clinical features are reflected in shared neurobiological substrates.<sup>101</sup> Based on a meta-analyses of 226 relevant studies in mood and anxiety disorders, alterations in brain functioning were found to be similar and correlated with cognitive deficits and negative emotions (ie, transdiagnostic convergence). These results suggest that the symptoms of mood and anxiety disorders are associated with similar neurobiological patterns.<sup>101</sup> Of note, although ADHD was not included in this meta-analysis, many of the ADHD-related neurobiological alterations discussed above are consistent with those observed for mood and anxiety disorders, lending support for the pathophysiological overlap between ADHD and these comorbidities.<sup>41,102</sup>

**KEY TAKEAWAY:** Multiple brain networks are involved in attention, with reduced function of these networks associated with symptoms and characteristics of ADHD, including deficits in sustained attention, response inhibition, executive function, and emotional control.

### ALTERED NEUROTRANSMISSION IN ADHD

In addition to studies implicating candidate genes regulating NE and DA synthesis and breakdown in ADHD, imaging studies have provided further supportive evidence of catecholamine and other neurotransmitter dysregulations in ADHD **(Table 3)**.

| Table 3. Potential Neurotransmitters Involved in ADHD <sup>52,103-107</sup> |  |  |
|---|--|--|
| Neurotransmitter  | Attention-related functions  |  |
| DA  | Planning and initiation of motor<br>response, reaction to novelty,<br>processing of reward |  |
| NE  | Arousal modulation, cognitive processing   |  |
| 5-HT  | Management of depression, anxiety, and sleep; emotional regulation                         |  |
| GABA  | Motor control, behavioral inhibition   |  |
| Glu   | Learning, memory   |  |

5-HT, serotonin; ADHD, attention deficit/hyperactivity disorder; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; NE, norepinephrine.

Functional imaging studies, such as positron emission tomography and single-photon emission computed tomography, which use selective ligands for the dopamine transporter (DAT), have reported increased DAT binding in up to 70% of children and adults diagnosed with ADHD, indicating a higher density of DAT in the brains of these individuals than in controls.<sup>2,108</sup> It is important to mention that this is not conclusive, as a number of studies have not found altered DAT binding in ADHD, and it is possible that medication status may explain some of the discrepancy.<sup>2,108</sup> Both reduced and elevated DA receptor D<sub>2</sub> availability, as well as reduced D<sub>2</sub> and D<sub>3</sub> binding in the striatum and nucleus accumbens, have also been noted, differentiating ADHD from control groups.<sup>2,108,109</sup>

Absence of appropriate **radioligands** for NE has limited imaging research into NE function in ADHD,<sup>2</sup> however, non-imaging evidence for NE dysfunction in ADHD comes from multiple other sources. Neurobiological evidence includes the abundance of the  $a_{24}$  adrenoceptor subtype in the

PFC<sup>110</sup> and enhanced PFC functioning following stimulation of postsynaptic  $a_{2A}$  receptors by NE.<sup>111</sup> Genetic studies have found an association between a variation in the gene encoding for dopamine ß hydroxylase, resulting in reduced NE synthesis<sup>112</sup> and deficits in sustained attention.<sup>113,114</sup> The role of NE dysfunction in the pathogenesis of ADHD is also supported by the fact that all US Food and Drug Administration-approved medications for ADHD have either direct or indirect effects on NE, presumably leading to improvement of PFC function.<sup>114</sup> Peripheral levels of NE, monoamine oxidase, and the NE metabolite, 3-methoxy-4-hydroxyphenyl-ethylene glycol, are being studied as biomarkers that could differentiate individuals with ADHD from controls, as well as reflect symptom severity and predict treatment response.115

Evidence of catecholamine dysfunction in ADHD lends further credibility to the pathophysiological hypothesis implicating prefrontal cortical, caudate, and cerebellar dysfunction. Studies have found that the PFC is especially sensitive to its neurochemical environment, particularly DA and NE signaling.<sup>111</sup> These catecholamines are so critical to the function of the PFC that either too little or too much neurotransmitter results in impaired functioning.<sup>15,116</sup> In fact, DA and NE regulate the activity of prefrontal pathways in an inverted u-shaped dose-response manner (Figure 6).<sup>111</sup> Namely, hypoactive and hyperactive catecholamine signaling in these circuits (including excessive DA signaling due to stress or an excessive dose of a stimulant medication) can cause disruption in attention, impulse control, and executive function.<sup>15,111</sup> This has ramifications for ADHD treatment, as currently approved pharmacotherapies (both stimulants and nonstimulants) correct for catecholamine imbalance in the PFC.<sup>116</sup>

As was the case with catecholamines, studies have pointed to involvement of variations of genes in the regulation of Glu signaling.<sup>42</sup> Further supporting



### Figure 6. Catecholamine levels and PFC function (adapted from Arnsten 2009).<sup>111,117</sup>

DA, dopamine; NE, norepinephrine; PFC, prefrontal cortex.

Note: Optimal NE levels also engage  $\alpha_{_{1\prime}}$  associated with wakefulness and alertness.  $^{\scriptscriptstyle 118}$ 

these findings, a proton magnetic resonance spectroscopic (MRS) study reported reduced Gluglutamine (Glx) concentrations in the striatum of participants with ADHD relative to controls. Interestingly, lower basal ganglia Glx was significantly correlated with greater symptom severity in the ADHD group.<sup>119</sup> Gamma-aminobutyric acid (GABA) has also been implicated in ADHD, with an MRS study reporting reduced GABA concentrations in somatosensory and motor cortices of participants with ADHD compared with controls, possibly reflecting deficient intracortical inhibition in ADHD.<sup>104</sup>

Serotonin also appears to play a role in ADHD. Functional brain imaging of 5-HT binding and platelet 5-HT binding in individuals with ADHD have yielded inconsistent results,<sup>109</sup> most likely supporting the biological heterogeneity of ADHD. Furthermore, we previously mentioned that  $a_{2A}$  adrenoceptors are implicated in the pathophysiology of ADHD: not only are  $a_{2A}$  adrenoceptors in the PFC involved in regulation of NE release, but they are also involved in the modulation of 5-HT synthesis and release.<sup>120</sup> Moreover, data suggest that 5-HT signaling increases DMN activity, a known imaging finding in ADHD.<sup>121</sup> Studies of the 5-HT transporter (SERT) and the main 5-HT metabolite (5-hydroxyindoleacetic acid [5-HIAA]) also provide evidence for the role of 5-HT in ADHD. For example, in boys with ADHD, cerebrospinal fluid levels of 5-HIAA have been positively correlated with symptoms of hyperactivity,<sup>122</sup> and increased affinity for platelet SERT binding has been found to correlate with poor attention (ie, response inhibition), impulsivity, and aggression.<sup>109</sup>

Turning once again to mood and anxiety disorders, studies have shown alterations in 5-HT, DA, and NE,<sup>123,124</sup> neurotransmitters involved in emotional regulation, cognition, and modulation of arousal **(Table 3)**.<sup>52,107,123,124</sup> As discussed above, alterations in these neurotransmitters have also been reported in ADHD, adding to the evidence of overlapping of the neurobiological underpinnings of these disorders.

**KEY TAKEAWAY:** Dysregulation of multiple neurotransmitters is implicated in ADHD, with balanced concentrations of DA and NE required for optimal functioning of the PFC.

### **CONCLUDING REMARKS**

In summary, ADHD is a complex, highly heritable, biologically heterogeneous condition involving slower maturation of long white matter tracts and decreased volume in brain regions relevant for sustained attention, impulse suppression, regulation of motoric activity, and executive function.<sup>39,54,66</sup> In addition to structural and functional brain changes, ADHD is associated with dysregulation of DA, NE, 5-HT, Glu-Glx, and GABA signaling.<sup>42,104,109,115,119</sup> Despite individual neurobiological variations, functional brain networks and the neurotransmitter systems that subserve them may present viable targets for future pharmacologic interventions, including individualized treatment approaches. Due to the multidimensional neurobiological overlap of ADHD with mood and anxiety disorders (ie, genetics, neuroimaging, neurotransmission),<sup>41,101,102,123,124</sup> novel ADHD treatments have the potential to address symptoms beyond those of pure ADHD.

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