Neurobiology, Circuits, and Genetics

Section 1: Symptoms and Circuits

In this chapter, the hypothetical pathophysiology underlying attention deficit hyperactivity disorder (ADHD) is discussed. Besides providing an overview of the main hypothesis underlying the symptoms of ADHD, such as problems with executive functioning, this chapter will also peruse old and new views on the environment-neurobiology interaction of this disorder. By giving a holistic view of the disorder, it will hopefully become clear that many different treatment options are available for every symptom of ADHD. Section 1 of Chapter 1 will focus on the symptoms of ADHD, and the circuits underlying these symptoms.

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Deconstructing the Syndrome into DSM-IV Diagnostic Symptoms

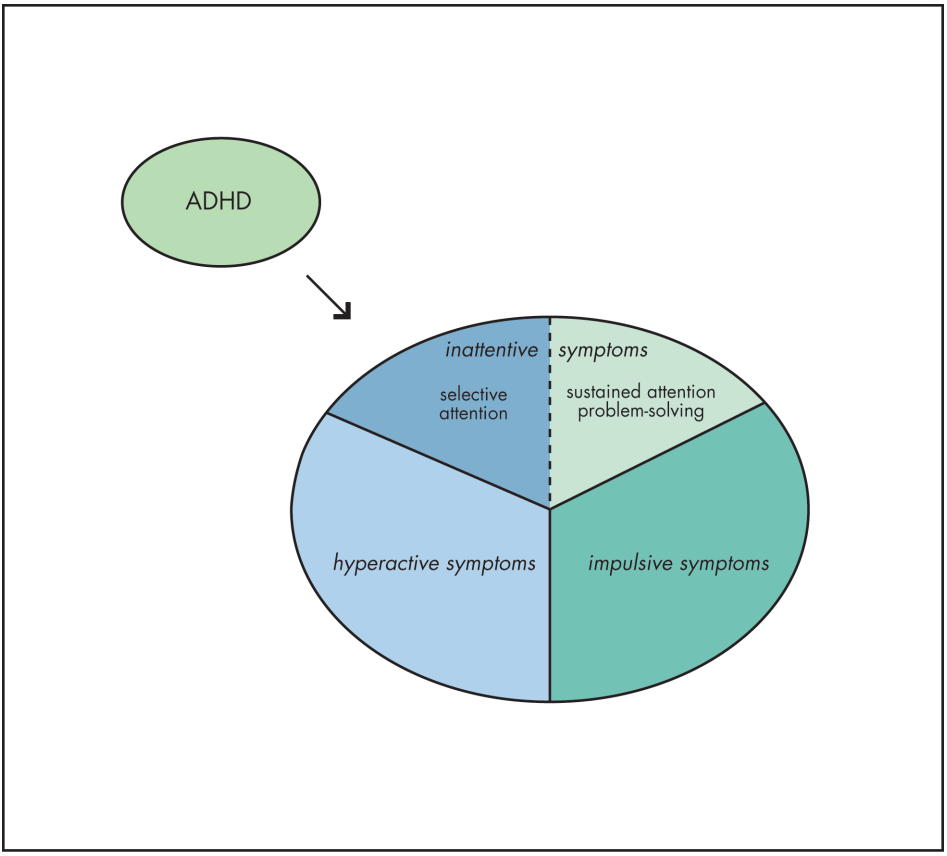

FIGURE 1.1. Attention deficit hyperactivity disorder (ADHD) is divided into three clusters of symptoms: hyperactive, impulsive, and inattentive. As each patient presents with a specific degree of impairment in these three categories, a patient can, according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), be cast into the following subtypes: the predominantly inattentive type, the predominantly hyperactive-impulsive type, and lastly the combined type, which is also the most frequent one.

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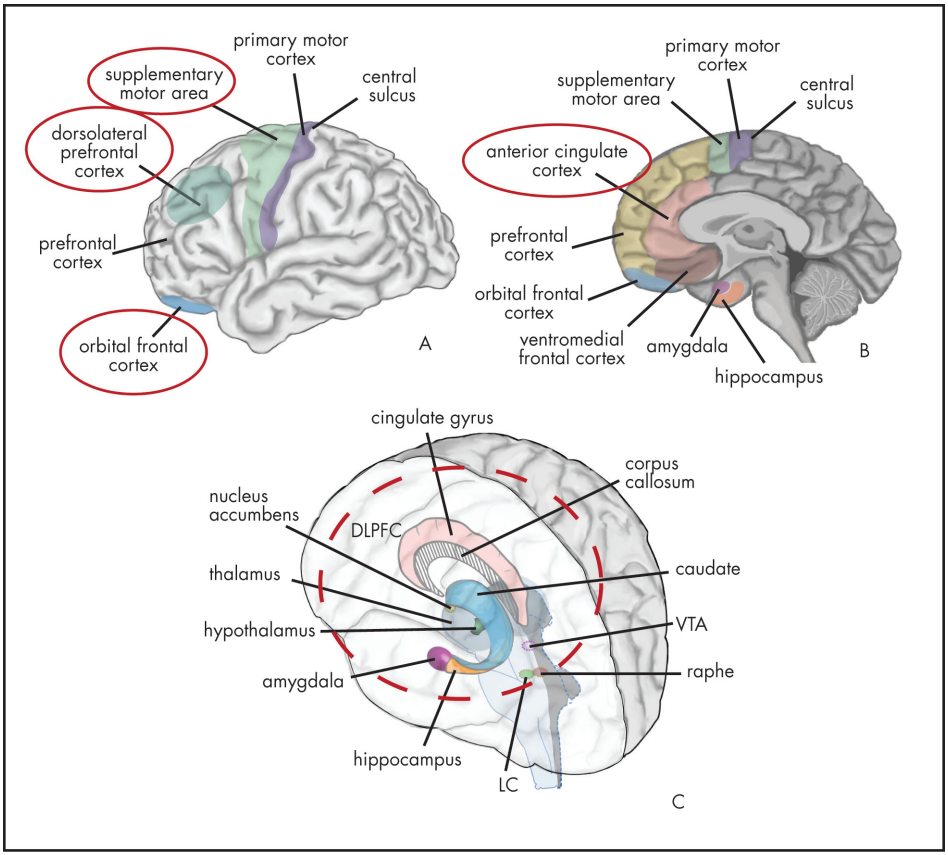
Important Brain Areas in Executive Function and Motor Control



LC: locus coeruleus; VTA: ventral tegmental area

FIGURE 1.2. To understand better the underlying pathophysiology of ADHD, it is important to know which brain circuits are affected and how they can impact other processes. At least four different brain regions (red circles in A and B) are affected in ADHD, and may lead to altered functioning of their respective cortical-striatal-thalamic-cortical (CSTC) loops (dotted red circle in C, and Figures 1.4), impacting executive functioning and motor control.

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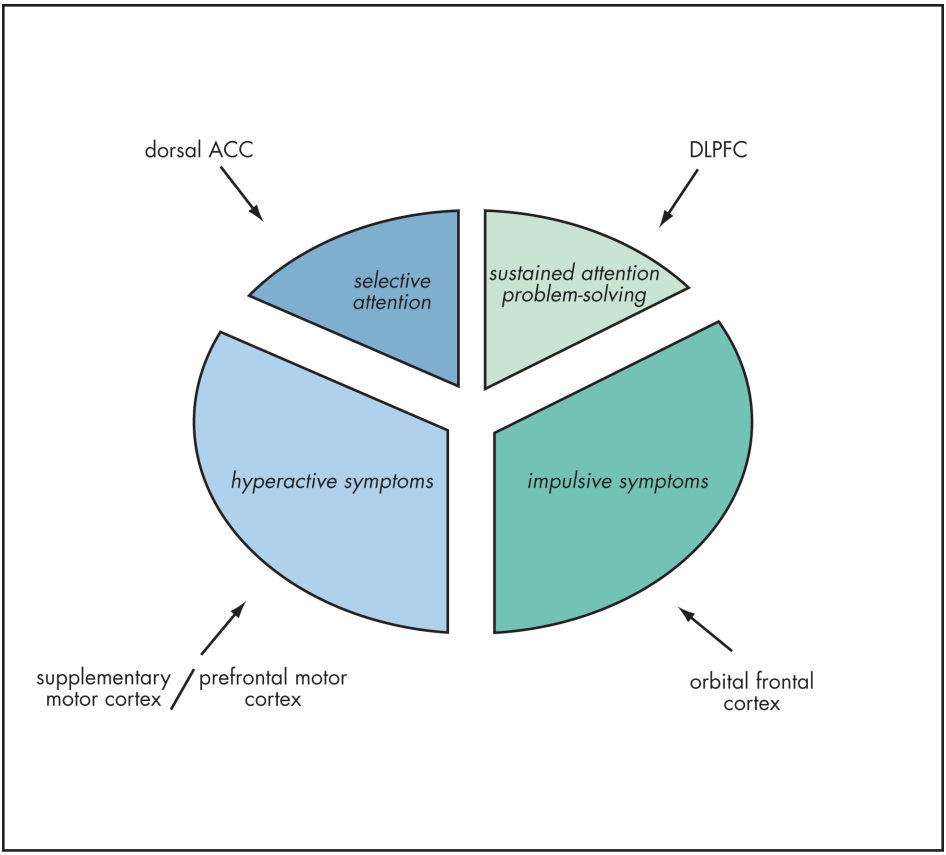
How Are Core Symptoms of ADHD Linked to a Malfunctioning Prefrontal Cortex?



ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex

FIGURE 1.3. Inefficient information processing in the brain areas shown in Figure 1.2 can hypothetically lead to the different symptoms of ADHD and other psychiatric disorders: malfunctioning of the dorsal ACC can result in problems with selective attention; malfunctioning of the DLPFC can result in problems with sustained attention; impairments in the supplementary motor cortex/prefrontal motor cortex can theoretically lead to symptoms of hyperactivity; impairments in the orbital frontal cortex can lead to impulsive symptoms. These various brain areas are part of a circuitry referred to as the cortical-striatal-thalamic-cortical loops, which are further explained in Figure 1.4.

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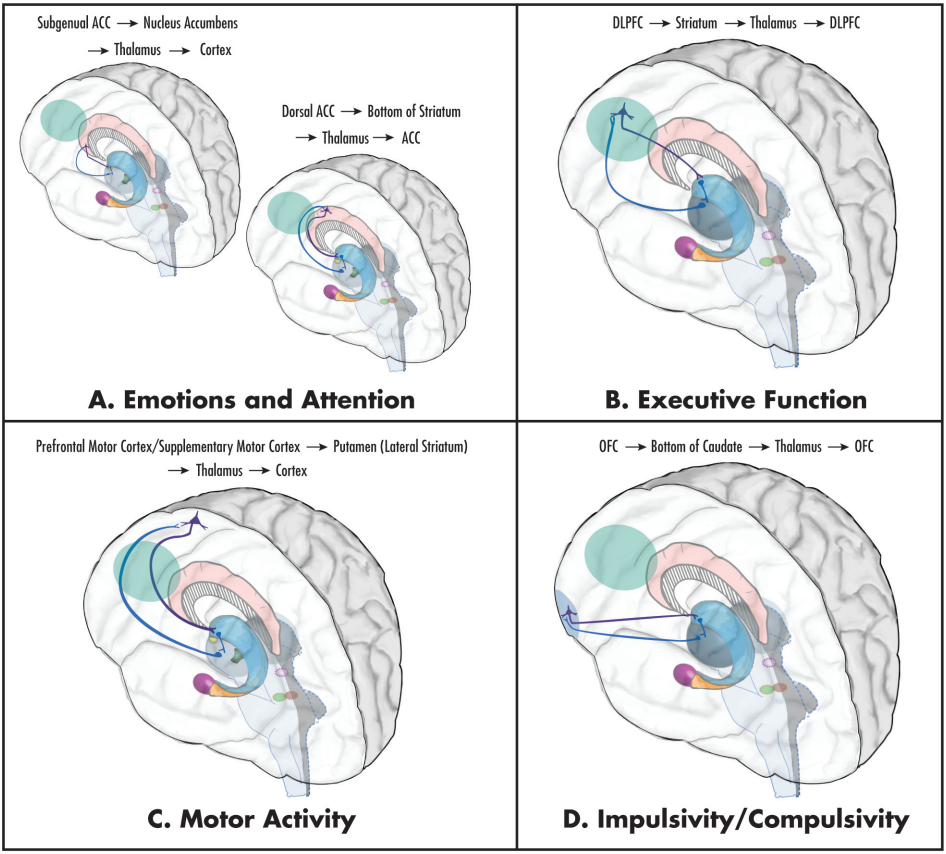
Hypothetical Malfunctioning CSTC Loops in ADHD



ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; NAcc: nucleus accumbens; OFC: orbital frontal cortex

FIGURE 1.4. (A) Emotions and attention are hypothetically regulated by the subgenual ACC–NAcc–thalamus loop and the dorsal ACC–bottom of striatum–thalamus loop, respectively. (B) Executive function is hypothetically regulated by the DLPFC–striatum–thalamus loop, and the prefrontal motor cortex–lateral striatum–thalamus loop hypothetically regulates motor activity (C). (D) Impulsivity and compulsivity are hypothetically regulated by the OFC–bottom of striatum–thalamus loop.

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The N-Back Test

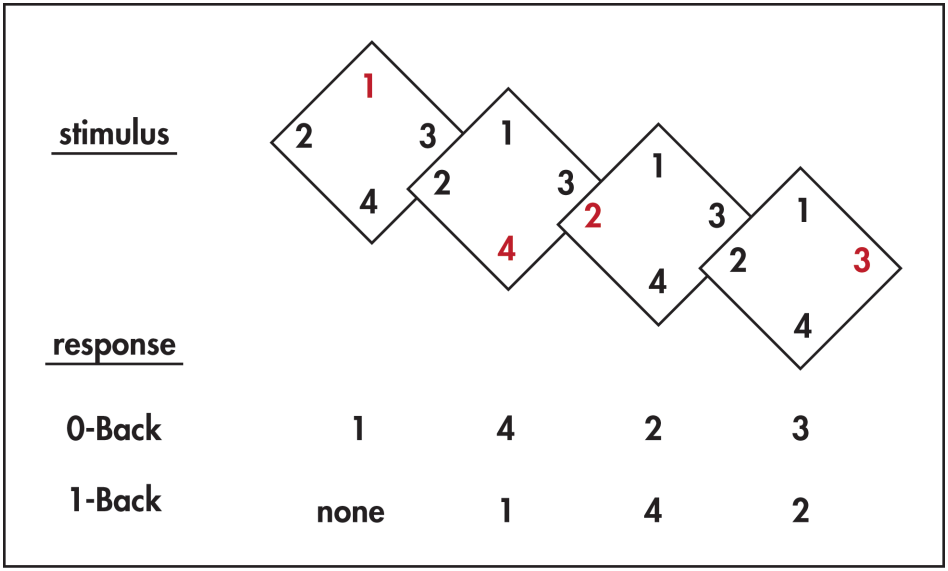

FIGURE 1.5. The N-Back test is used to assess executive function, especially sustained attention. In the 0-back variant, a participant looks at a number on the screen, and presses a button to indicate which number it is. In the 1-back variant, a participant only looks at the first number; when the second number appears the participant is supposed to press a button corresponding to the first number. Higher "N" numbers are correlated with increased difficulty in the test.

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Assessing Sustained Attention and Problem-Solving With the N-Back Test

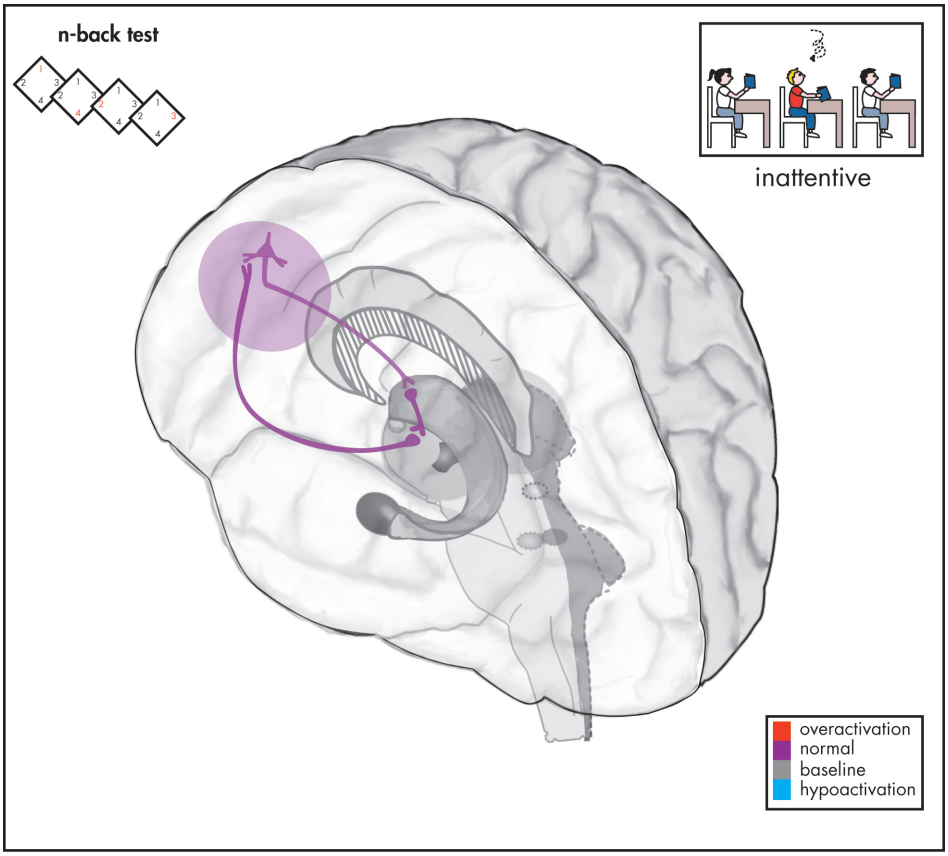

FIGURE 1.6. The level of activation of the dorsolateral prefrontal cortex (purple circle) can be assessed using the N-back test. As shown in Figure 1.4B, executive function, especially sustained attention, is hypothetically associated with the following CSTC loop: DLPFC–striatum–thalamus. Inefficient information processing within this loop would theoretically cause a person to lack sustained attention on a task and have problems with organization, follow-through, and problem-solving.

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Symptom Overlap Among Many Psychiatric Syndromes

symptom	*psychiatric syndromes with the same overlapping symptoms*		
 problems concentrating	major depression	ADHD	narcolepsy

FIGURE 1.7. Concentration problems are symptoms of many disorders besides ADHD. The dimensional approach suggests to deconstruct psychiatric disorders into symptoms, and treat the symptoms rather than the disorder (see also Table 1.1).

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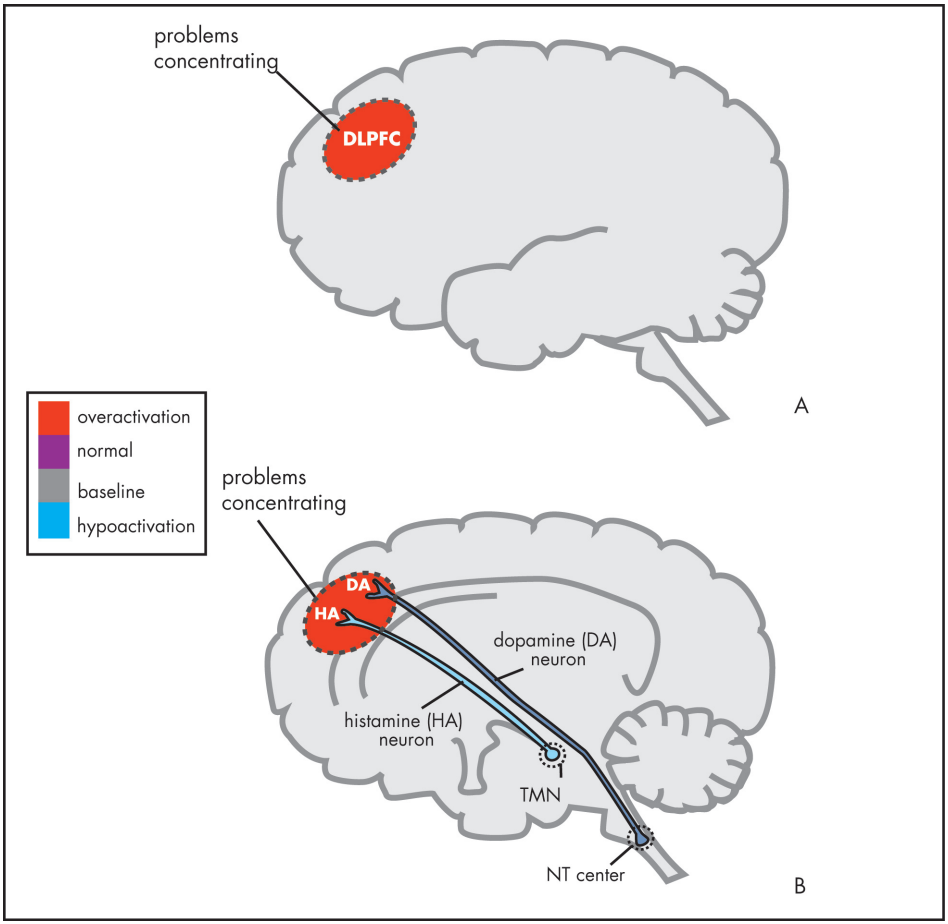

DA: dopamine; DLPFC: dorsolateral prefrontal cortex; HA: histamine; TMN: tuberomammillary nucleus; NT: neurotransmitter

FIGURE 1.8. Once a malfunctioning circuit has been exposed, the appropriate treatment can be selected based on the neurotransmitter system involved in that circuitry (A). For example, problems concentrating are hypothetically linked to the DLPFC, which is regulated by dopamine (DA) and histamine (HA), thus treatments affecting DA or HA neurotransmission could potentially improve concentration (B).

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The Stroop Task

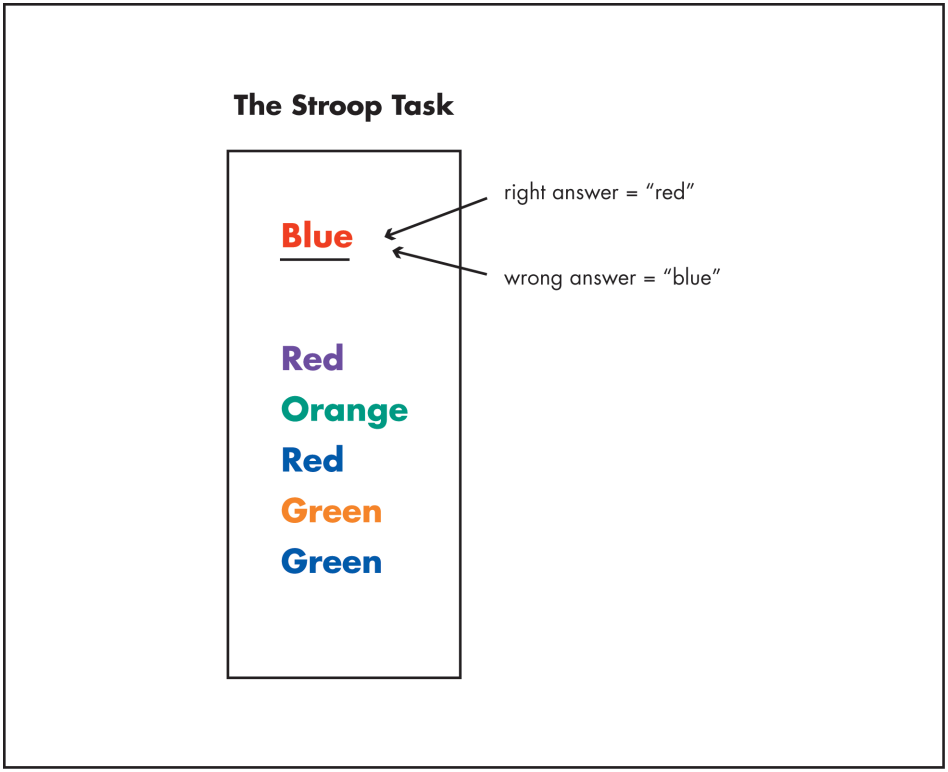

FIGURE 1.9. The Stroop task is used to assess selective attention, and requires the participants to name the color with which a word is written, instead of saying the word itself. In the present case, for example, the word "blue" is written in red. The correct answer is therefore "red," while "blue" is the incorrect choice.

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Assessing Selective Attention With the Stroop Task

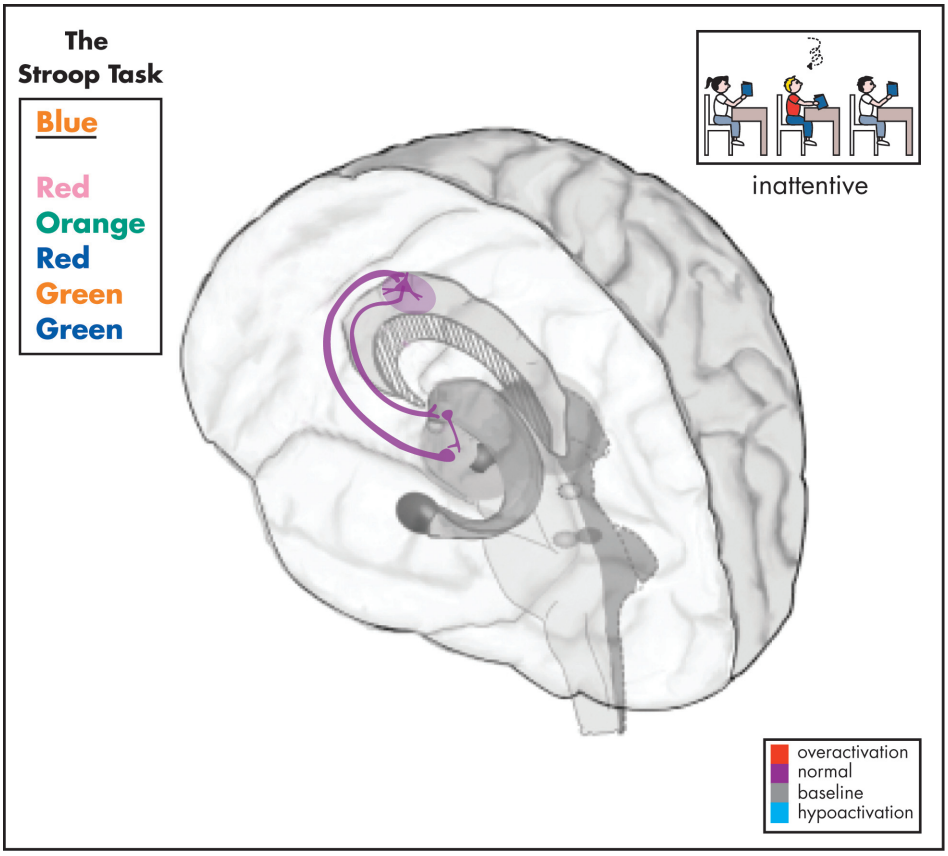

FIGURE 1.10. The level of activation of the anterior cingulate cortex (purple circle) can be determined using the Stroop task. As shown in Figure 1.4A, selective attention is hypothetically associated with the ACC–striatum–thalamus CSTC loop. Inefficient information processing within this loop would theoretically cause a person to pay little attention to detail, make careless mistakes, not listen, be distracted, and lose valuables.

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Impulsivity is Modulated by the Orbital Frontal Cortex

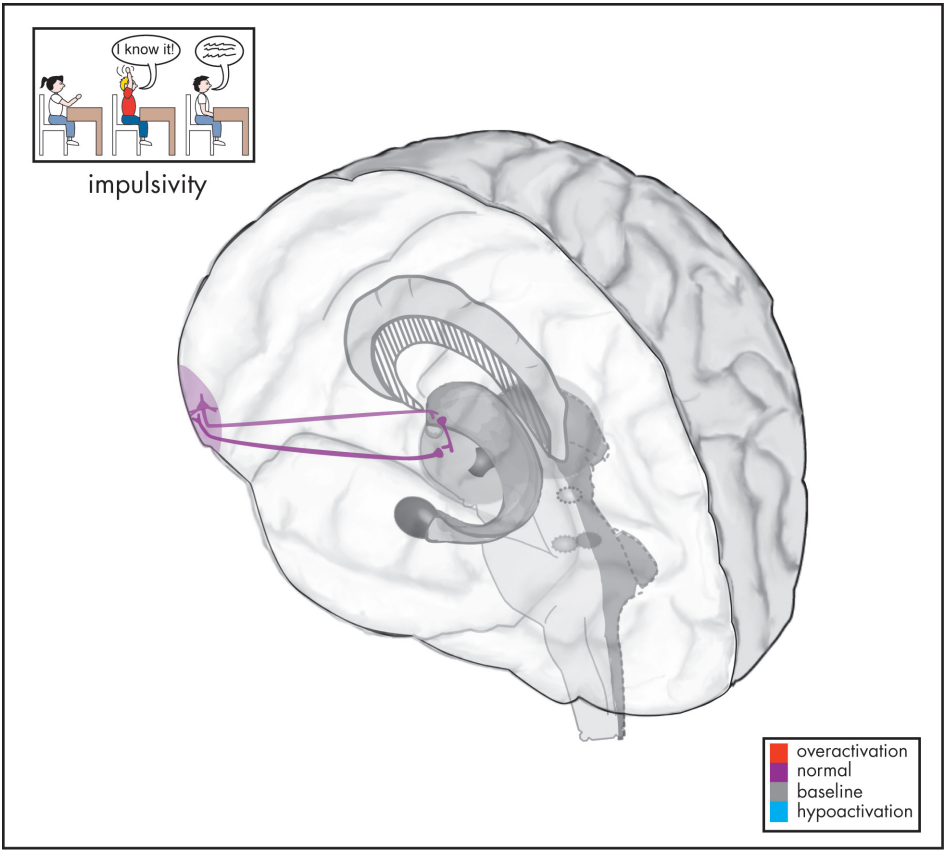

FIGURE 1.11. As shown in Figure 1.4D, impulsivity is hypothetically associated with the orbital frontal cortex (purple circle)–bottom of striatum–thalamus CSTC loop. Inefficient modulation within this loop would theoretically cause a person to talk excessively, blurt things out, not wait in line, and interrupt others.

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Motor Hyperactivity is Modulated by the Prefrontal Motor Cortex

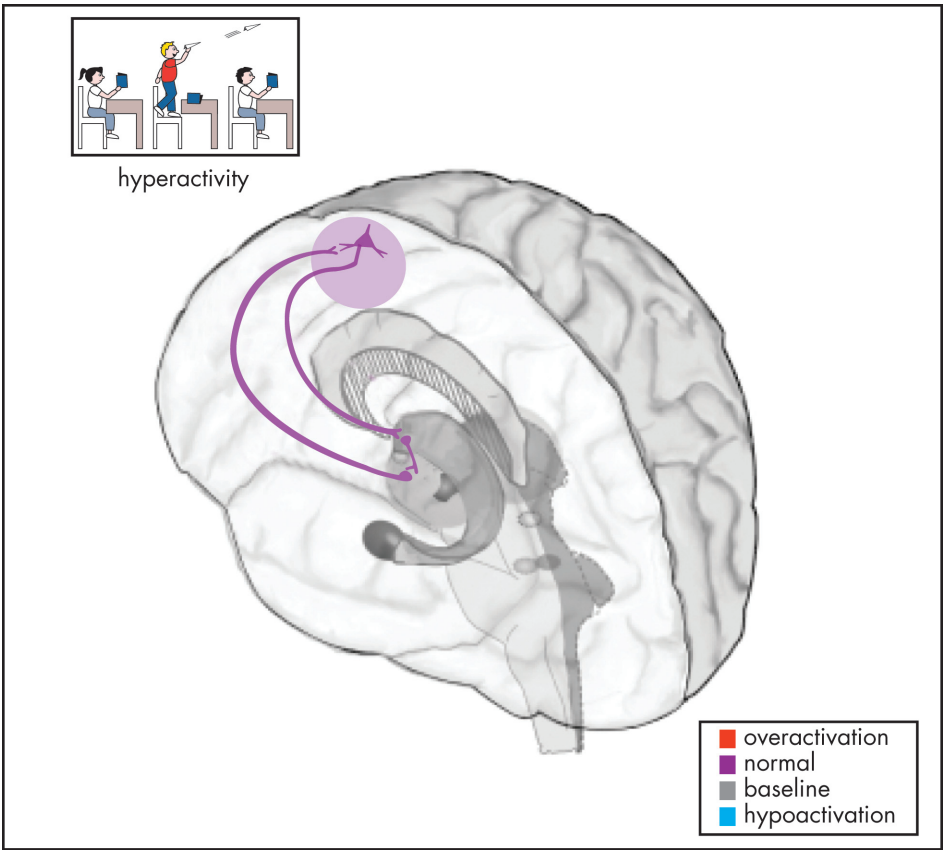

FIGURE 1.12. Motor hyperactivity is hypothetically associated with the supplemental motor cortex/prefrontal motor cortex (purple circle)–lateral striatum–thalamus CSTC loop, as shown in Figure 1.4C. Gross motor hyperactivity is often more pronounced in children, and inefficient modulation within this loop would theoretically cause a child to fidget, leave his/her seat, run/climb, constantly be on the go, and have trouble playing alone. In adults, motor hyperactivity can be seen as internal restlessness and trouble sitting through meetings (more details on the difference in ADHD symptoms between children and adults can be found in Table 2.1).

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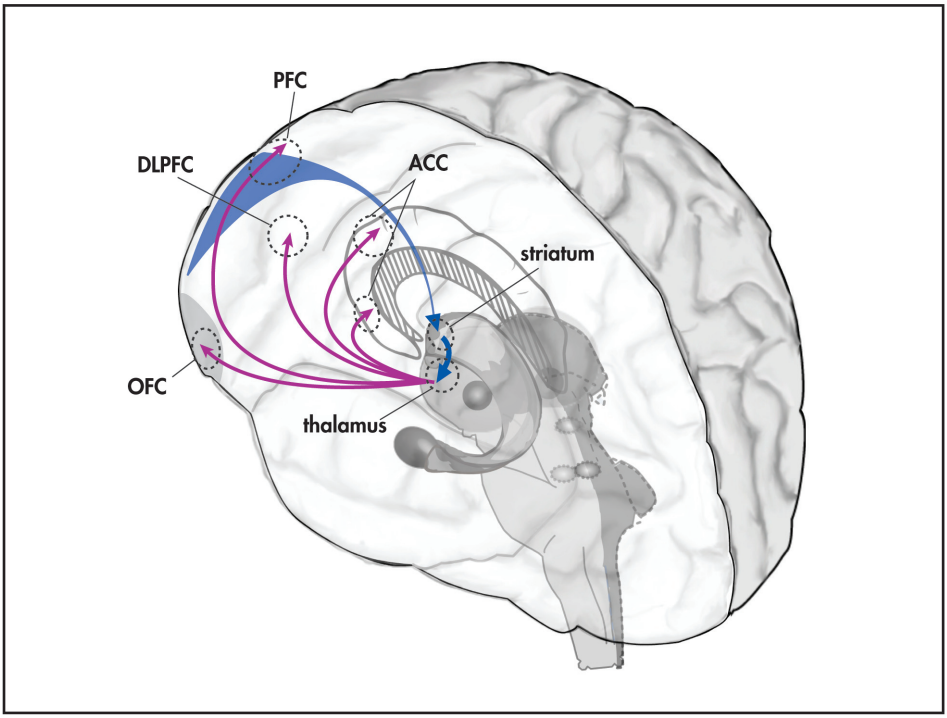
Interconnected Networks in ADHD



ACC: Anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex; PFC: prefrontal cortex

FIGURE 1.13. Not only does the prefrontal cortex regulate overt responses such as movement, but it also regulates covert responses such as attention. Thus the PFC is the main player in regulating attention, sustaining attention, and inhibiting the processing of irrelevant stimuli. People with lesions of the prefrontal cortex are distracted, lack concentration and organization, and act impulsively. As this figure exemplifies, all five CSTC loops are interconnected. This can explain why different magnitudes of alterations in any of those circuits can result in varying degrees of impairment in attention, impulsivity, and hyperactivity.

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What is Normal Cognitive Function?

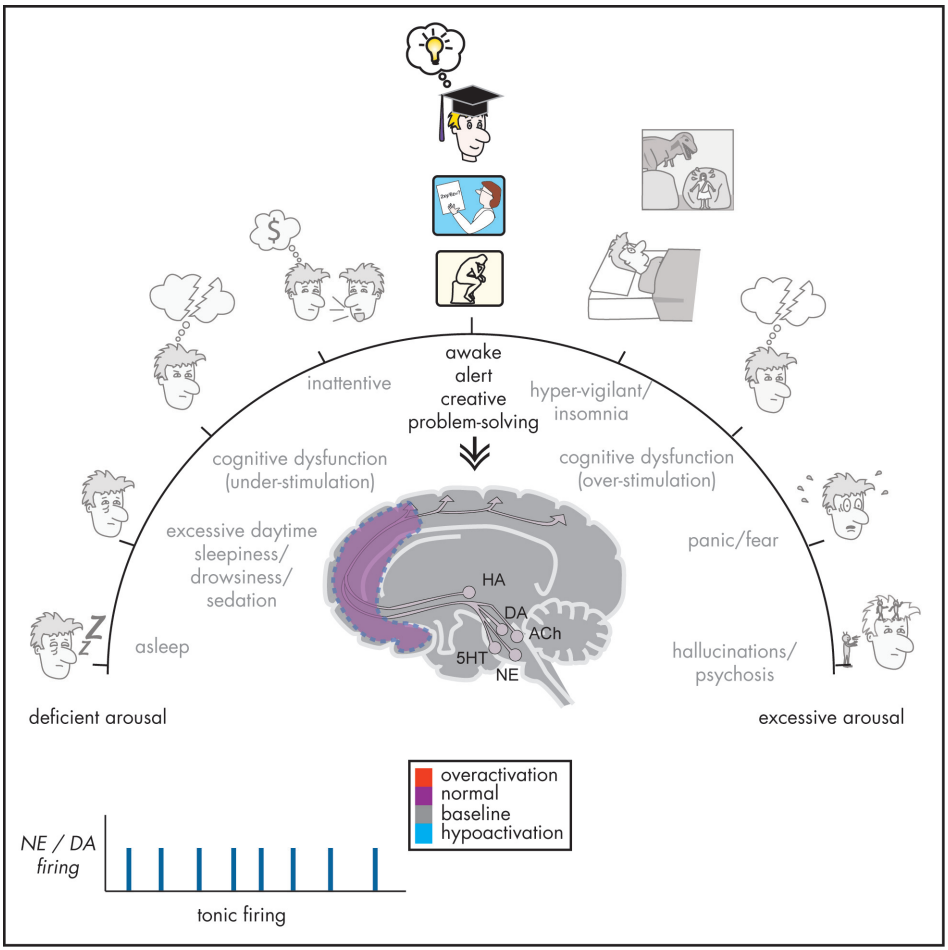

FIGURE 1.14. Proper functioning of the prefrontal cortex is imperative in tasks such as remaining awake and alert, being creative, and being able to solve problems. The networks regulating these tasks are the same as the ones involved in arousal, attention, fear, mood, and hallucinations—and they all rely on a finely tuned prefrontal cortex. Any aberration in these networks can tilt the balance toward deficient (to the left) or excessive (to the right) arousal. As Figures 1.17 and 1.19 will show, the symptoms of ADHD could hypothetically be caused by deficient and/or excessive arousal networks, and most likely result from altered firing patterns in DA and NE neurons.

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Baseline NE and DA Neuronal Firing is Tonic

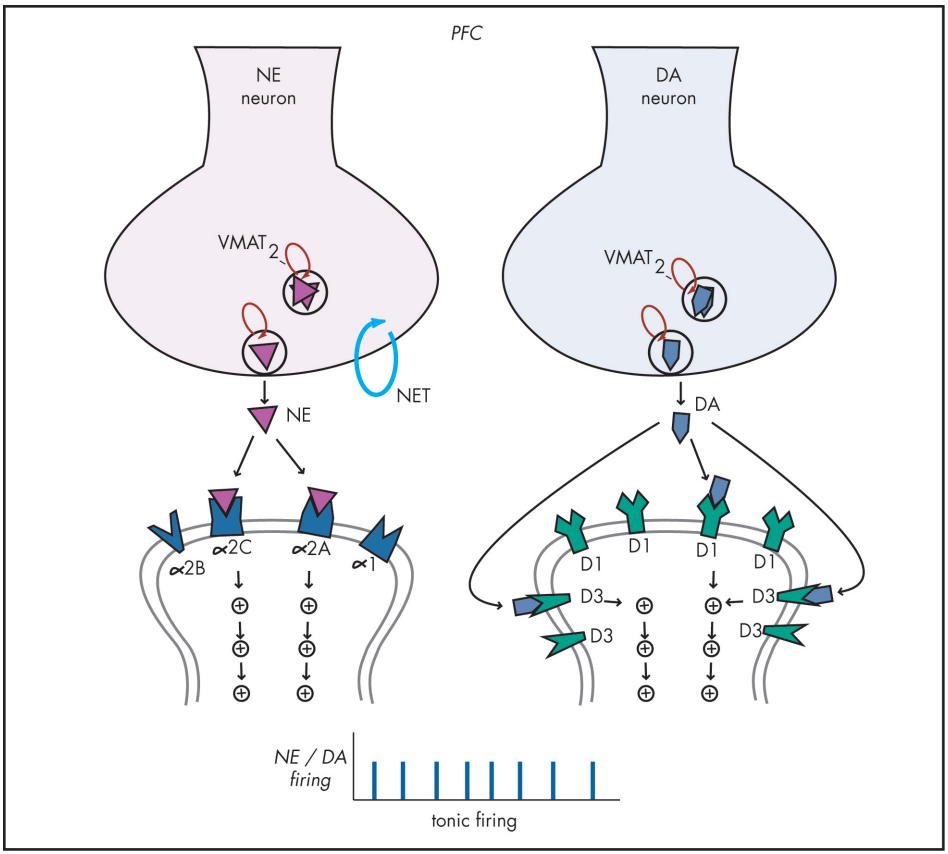

FIGURE 1.15. Modulation of prefrontal cortical function, and therefore regulation of attention and behavior, rely on the optimum release of catecholamines. Under normal conditions, released NE and DA in the prefrontal cortex stimulate a few receptors on postsynaptic neurons allowing for optimal signal transmission and neuronal firing. At modest levels, NE can improve prefrontal cortical function by stimulating postsynaptic alpha2A receptors, but will lead to impaired working memory at high levels when alpha1 and beta1 receptors are also recruited. Similarly, modest levels of DA will first stimulate D3 receptors as these are more sensitive to DA than D1/2 receptors. Low to moderate, but not high, levels of D1 receptor stimulation can be beneficial to prefrontal cortical functioning. In the case of both DA and NE systems, moderation is certainly key (see Figure 1.21).

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Salience Provokes Phasic DA Neuronal Firing in Reward Centers

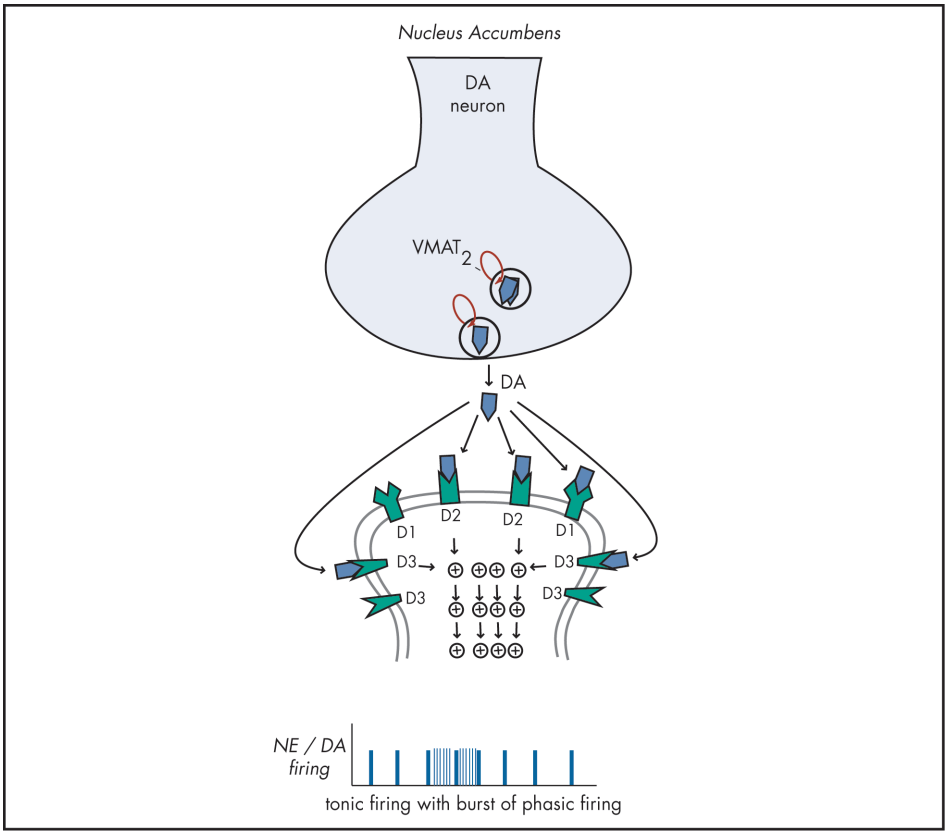

FIGURE 1.16. While tonic firing, as seen in the prefrontal cortex, is often preferred in neuronal systems, a little bit of phasic firing of DA neurons in the nucleus accumbens can be a good thing. Phasic firing will lead to bursts of DA release and when this happens in a controlled manner it can reinforce learning and reward conditioning, which can provide the motivation to pursue naturally rewarding experiences such as education, recognition, career development, enriching social and family connections, etc. When this system, however, is out of bounds, it can induce uncontrolled DA firing that reinforces the reward of taking drugs of abuse, for example, in which case the reward circuitry can be hijacked and impulses are followed uncontrollably. Thus, finely tuning the DA reward pathway in the nucleus accumbens and its connections to the amygdala and prefrontal cortex by ascertaining a low level of phasic firing in relation to tonic firing will theoretically lead to proper functioning of this complex system.

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Cognitive Function in ADHD:
Is It Deficient?

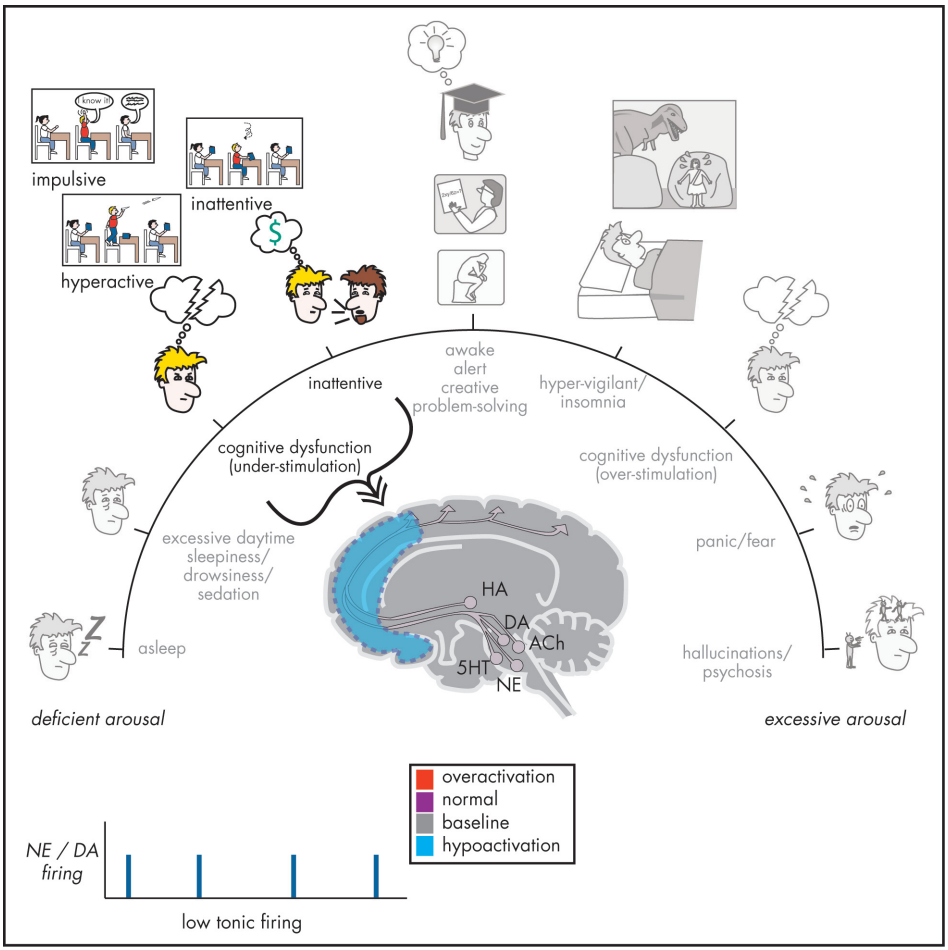

FIGURE 1.17. The underlying neurobiology of ADHD may be linked to the arousal pathways of the brain. Some patients with ADHD may have hypothetically deficient arousal networks which can lead to inefficient information processing via defective inhibitory pathways. Hypoactivity in the frontal part of the brain is associated with low tonic firing of both NE and DA neurons, and the symptoms associated with this can include inattentiveness and cognitive dysfunction. It has been hypothesized that stimulants are beneficial in the treatment of ADHD, because they can bring the activity of the neurotransmitters in those circuits back to normal.

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ADHD and Deficient Arousal:
Weak NE and DA Signals

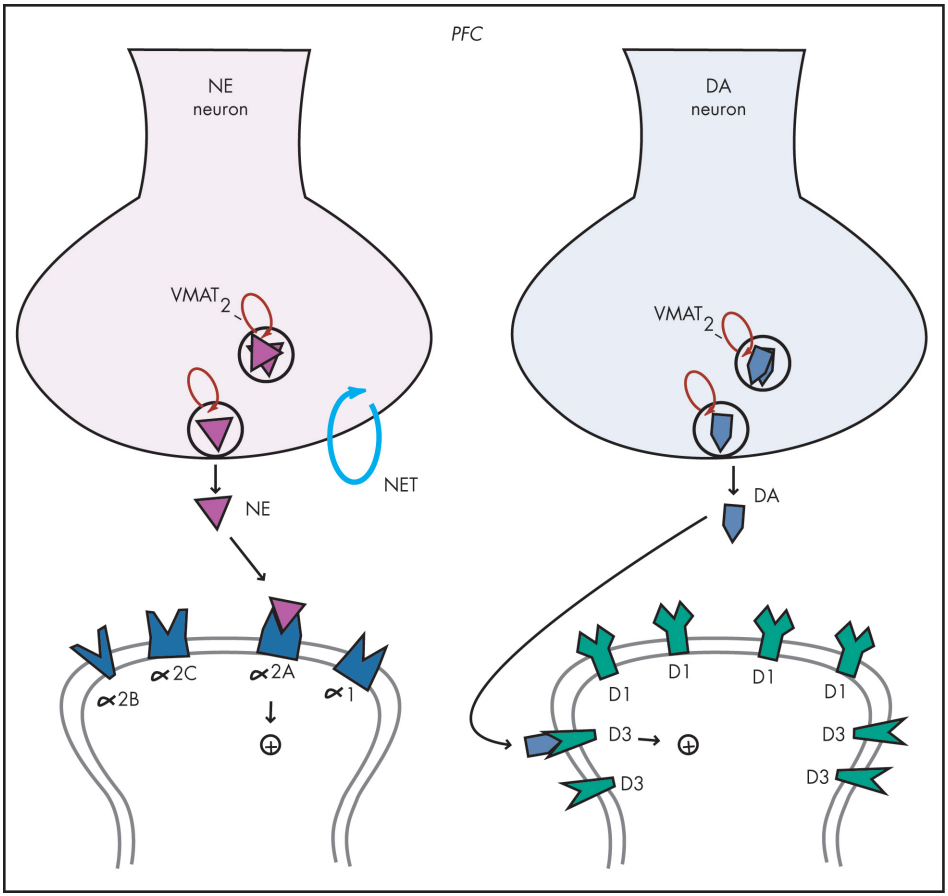

FIGURE 1.18. Besides being a key player in the arousal pathways, the prefrontal cortex is also the main brain area where imbalances in NE and DA systems hypothetically occur in ADHD. At the neuronal level, deficient signaling in prefrontal cortical DA and NE pathways is reflected by decreased neurotransmission and thus reduced stimulation of postsynaptic receptors. Agents that can lead to (1) increased release of these two neurotransmitters, or (2) increased tonic firing of these neurons, will be hypothetically beneficial in patients with ADHD by bringing prefrontal activity back to optimal level.

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Cognitive Function in ADHD:
Is It Excessive?

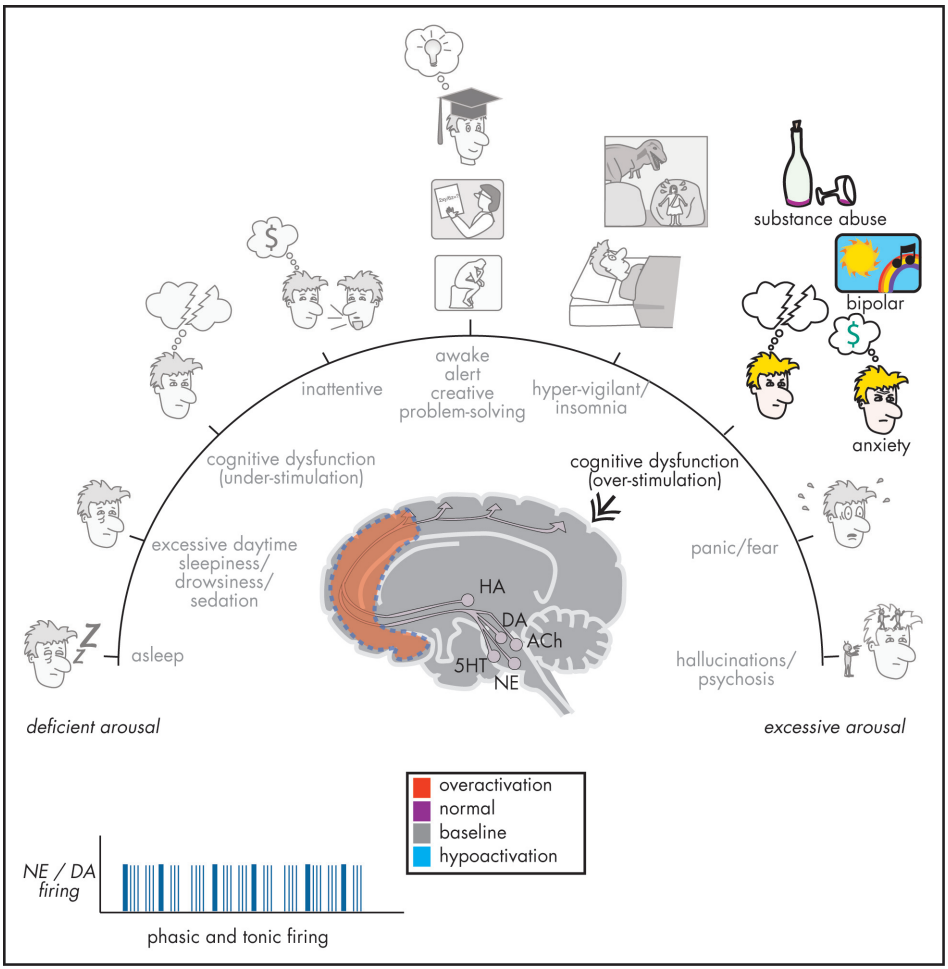

FIGURE 1.19. Excessive arousal mechanisms are theoretically as disruptive as deficient ones, since they will also lead to deteriorating signal-to-noise ratios. Hyperarousal can often be associated with chronic stress and comorbidities such as anxiety, and is characterized by increased tonic and phasic firing of prefrontal NE and DA neurons. In general, it is safe to say that in the arousal spectrum, the prefrontal cortex is "out of tune" and needs to be set back to normal. Both stimulant and non-stimulant medications can, via differing mechanisms, normalize the prefrontal cortex.

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ADHD and Excessive Arousal:
Impact of Stress and Comorbidities

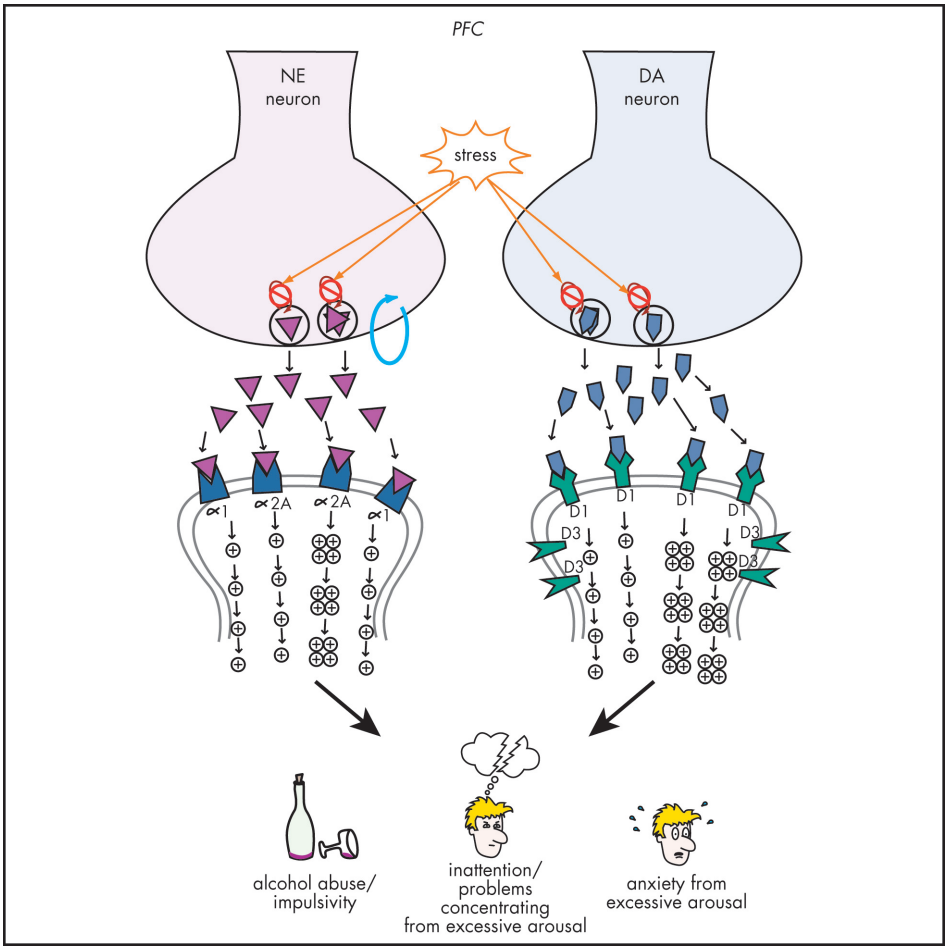

FIGURE 1.20. Non-treated adults with ADHD can often be stressed as they are trying to deal with their disorder while at the same time attempting to accomplish as much as their peers. Unfortunately, stress can activate NE and DA circuits in the prefrontal cortex, leading to high levels of catecholamine release and thus cause an excess of phasic NE and DA firing (see Figure 1.19). This excessive NE and DA neurotransmission may be the underpinning of the development of drug and alcohol abuse, impulsivity, inattention, and anxiety, all comorbid with ADHD. This emphasizes the notion that treatment of all comorbid disorders is necessary to ascertain good patient outcome.

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Cognitive Function in ADHD is Out of Tune:

Either Deficient or Excessive With Maladaptive Signal-to-Noise Ratios

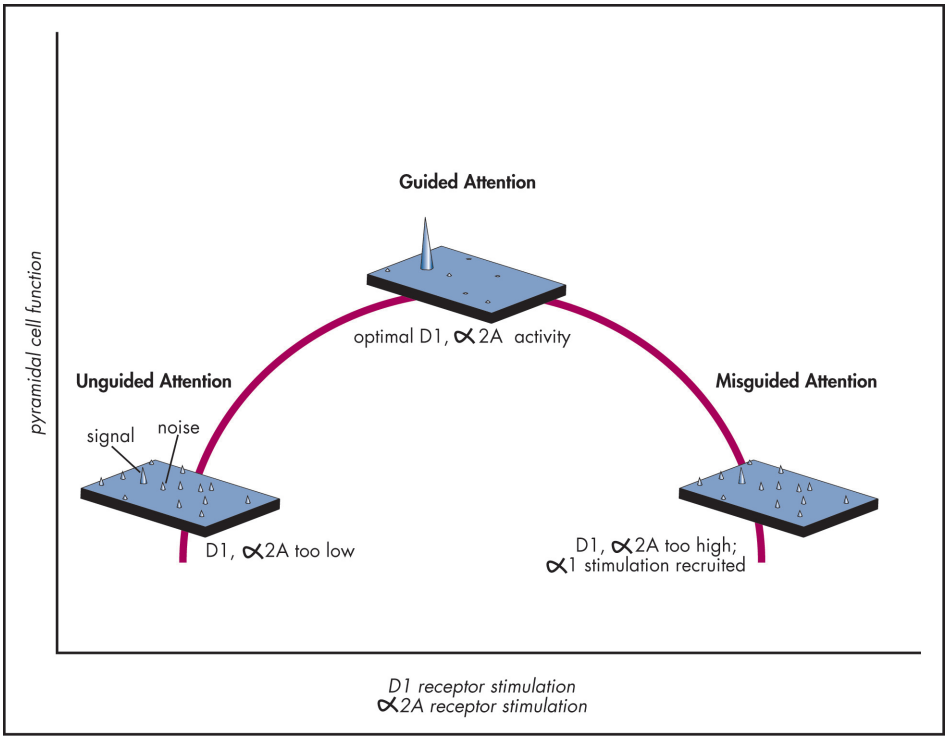

FIGURE 1.21. In order for the prefrontal cortex to work properly, cortical pyramidal neurons need to be tuned, meaning that moderate stimulation of alpha2A receptors by NE and D1 receptors by DA is required. In theory, the role of NE is to increase the incoming signal by allowing for increased connectivity of the prefrontal networks, while the role of DA is to decrease the noise by preventing inappropriate connections from taking place. Pyramidal cell function is optimal at the top of this inverted U-shaped curve, when stimulation of both alpha2A and D1 receptors is moderate. If stimulation at alpha2A and D1 receptors is too low (left side), all incoming signals are the same, preventing a person from focusing on one single task (unguided attention). When stimulation is too high (right side), the signals get scrambled as additional receptors are recruited, again misguiding a person's attention. Figures 1.22-1.26 will exemplify why a balanced stimulation of alpha2A and D1 receptors is so critical for correct interpretation of an incoming signal.

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Signal Distribution in a Dendritic Spine

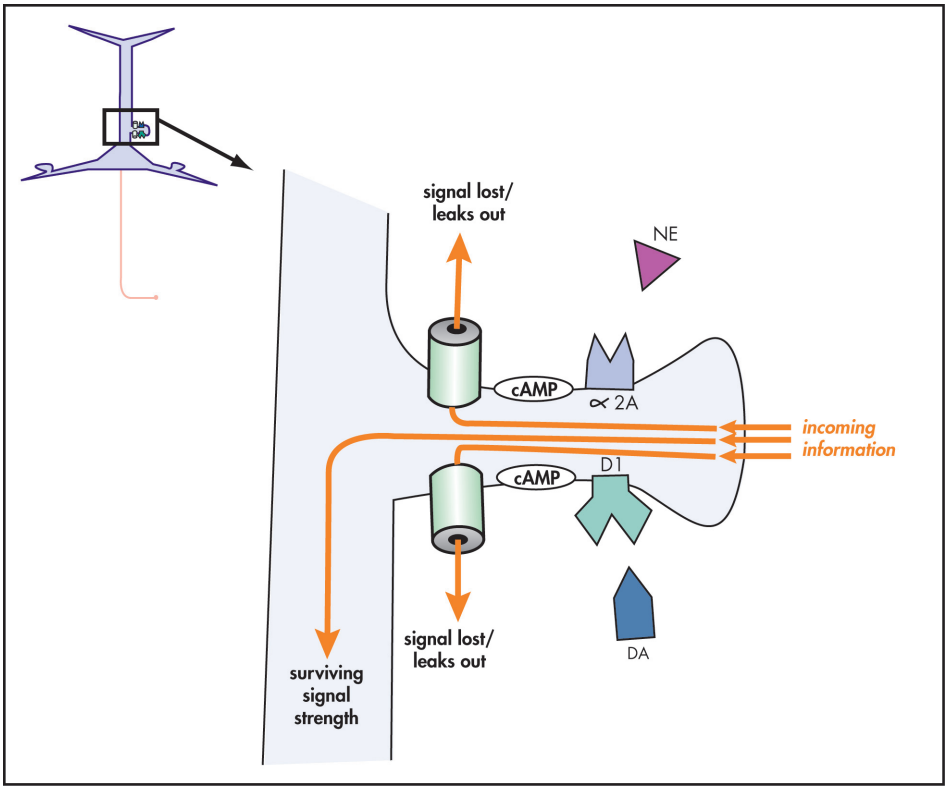

FIGURE 1.22. In the prefrontal cortex, alpha2A and D1 receptors are often located on the spines of cortical pyramidal neurons, and can thus gate incoming signals. Alpha2A receptors are linked to the molecule cyclic adenosine monophosphate (or cAMP) via the inhibitory G protein, or Gi. D1 receptors, on the other hand, are linked to the cAMP signaling system via the stimulatory G protein, Gs. In either case the cAMP molecule links the receptors to the hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN channels). An open channel will lead to a low membrane resistance, thus shunting inputs out of the spine. In the presence of an open channel, the signal leaks out and is therefore lost. However, when these channels are closed, the incoming signal survives and can be directed down the neuron to strengthen the network connectivity of similar neurons and lead to the appropriate signal and response.

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NE Actions at Alpha2A Receptors Strengthen Signal

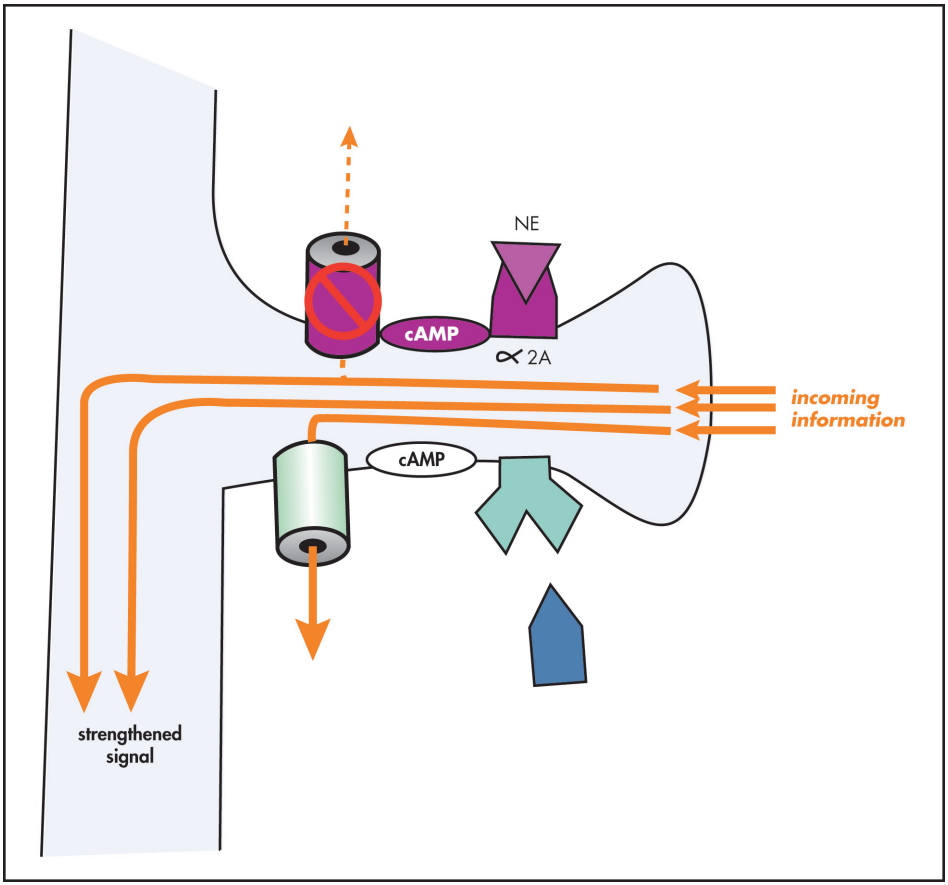

FIGURE 1.23. When NE, or a noradrenergic agonist, binds to an alpha2A receptor, the activated Gi-linked system inhibits cAMP thereby closing the HCN channel. Closure of the channel allows the signal to go through the spine and down the neuron, thereby strengthening network connectivity with similar neurons. So in general, in the prefrontal cortex, stimulation of alpha2A receptors will strengthen an incoming signal. By contrast, as will be seen in Figure 1.24 stimulation of D1 receptors will lead to weakening of the signal.

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DA Actions at D1 Receptors Weaken Signal

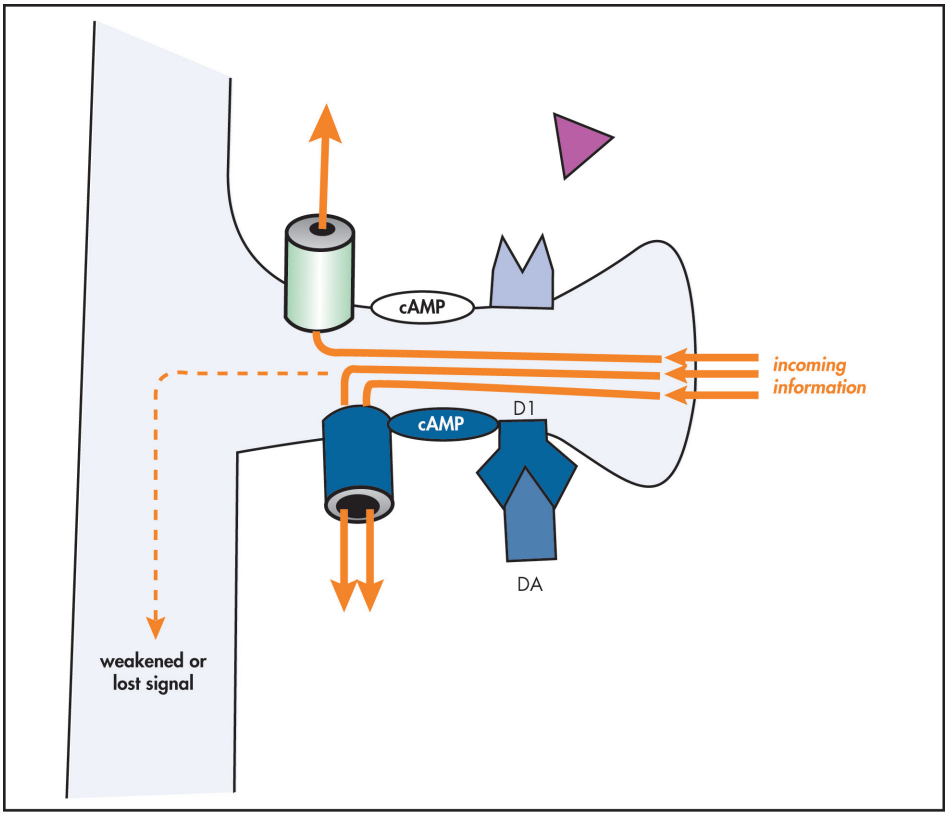

FIGURE 1.24. When DA, or a DA agonist, binds to a D1 receptor, the activated Gs-linked system will lead to increased stimulation—or opening—of HCN channels. The opening of the HCN channels, especially if excessive, will lead to leakage of the signal, thereby shunting any input out of the spine. So excessive stimulation of D1 receptors will, in contrast to stimulation of alpha2A receptors, result in the dissipation and/or weakening of a signal.

The mechanism of action of alpha2A (Figure 1.23) and D1 receptors explains in general why moderate stimulation of both types of receptors (Figure 1.21) is preferred in order to strengthen the signal-to-noise ratio in prefrontal cortical neurons (see Figure 1.25).

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How DA and NE Hypothetically "Tune" the PFC:
Signal Increased and Noise Reduced

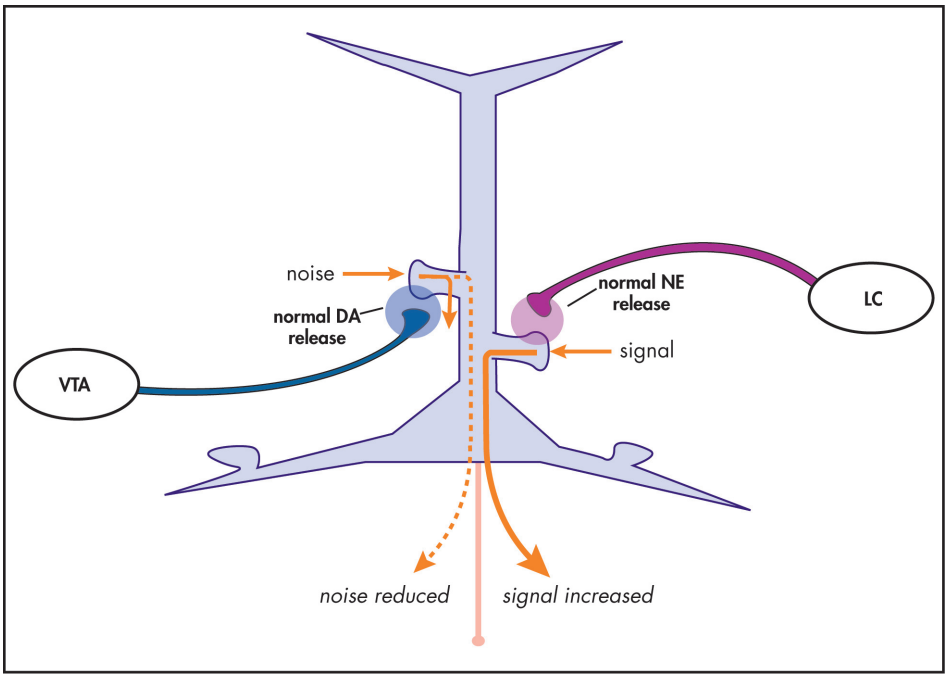

FIGURE 1.25. What happens following concurrent stimulation of alpha2A and D1 receptors by NE and DA, respectively? While the exact localization and density of alpha2A and D1 receptors within various cortical areas are still under intense investigation, it is possible to imagine the same pyramidal neuron receiving NE input from the LC on one spine and DA input from the VTA on another spine. If the systems are properly "tuned," then D1 receptor stimulation can reduce the noise and alpha2A receptor stimulation can increase the signal to result in proper prefrontal cortex functioning. Theoretically, this will result in adequate guided attention (Figure 1.21), focus on a specific task, and adequate control of emotions and impulses.

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How DA and NE Hypthetically "Tune" the PFC:

Low NE and Low DA: ADHD With Signals Reduced and Noise Increased

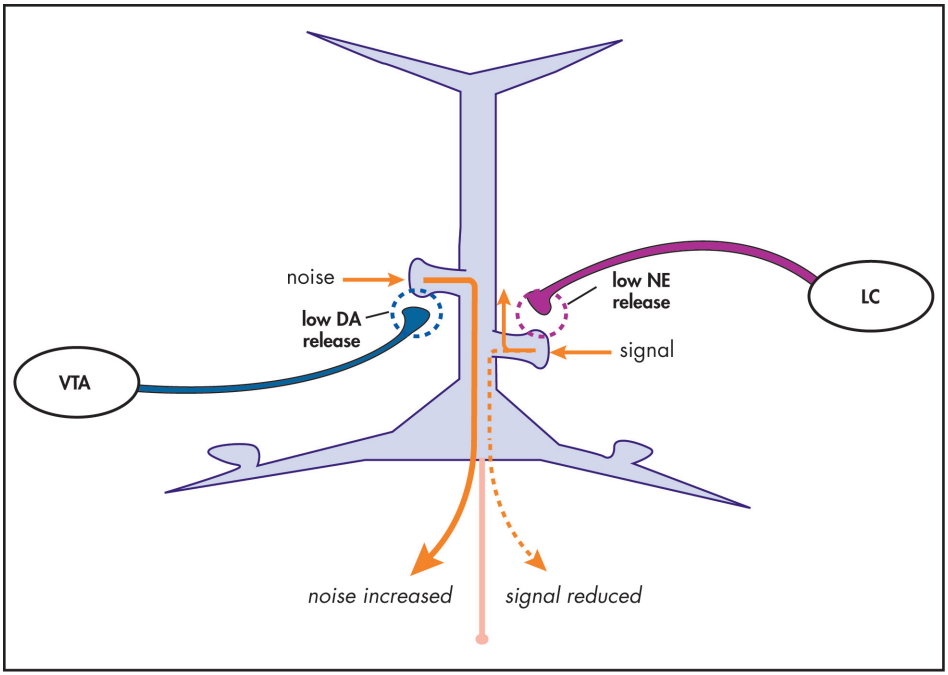

FIGURE 1.26. What happens, however, when there is low release of both DA and NE and thus low stimulation of both D1 and alpha2A receptors on the spines of these pyramidal neurons? A deficient DA and NE input will theoretically lead to increased noise and decreased signal, respectively, thus preventing a coherent signal to be sent. Hypothetically this could cause hyperactivity, or inattention, or both. If one neurotransmitter is low while the other is high, then a person could be exhibiting a whole different set of symptoms. By knowing both the levels of DA and NE neurotransmission and the specific area of the possible disturbances, it may one day be possible to predict the degree and type of symptoms from which a patient is ailing. With this in mind, Figures 1.27 and 1.28 will show how pyramidal neurons in different brain areas may be responsible for the different symptom presentation in ADHD.

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ADHD Core Symptoms:
Regional Problems of PFC "Tuning"

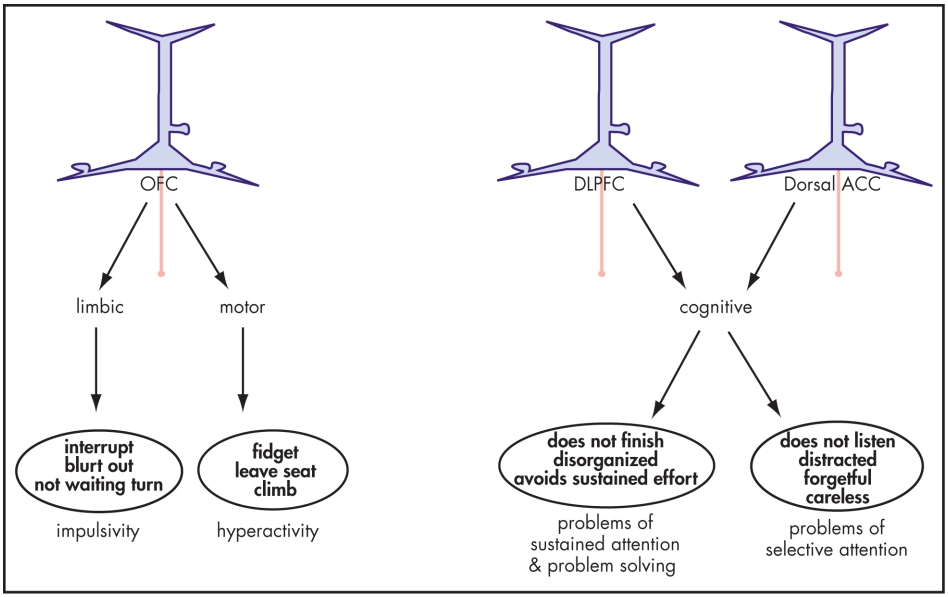

FIGURE 1.27. As shown in Figures 1.3. to 1.12, different brain areas are hypothetically important in the symptoms of ADHD. Alterations within the orbital frontal cortex are hypothesized to lead to problems with impulsivity or hyperactivity. Inadequate tuning of the DLPFC or the dorsal ACC can respectively lead to sustained or selective attentive symptoms. It is becoming increasingly clear that dysfunction in specific brain areas leads to specific symptoms, such that abnormalities in the orbitofrontal-limbic motivation networks have been observed in children with conduct disorder, while aberrations in the ventrolateral/dorsolateral fronto-cerebellar attention network have been observed in children with problems of sustained attention. Thus ongoing research may soon be able to map out specific symptoms to a specific brain area.

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ADHD and Comorbid Symptoms:
Additional Problems in the PFC

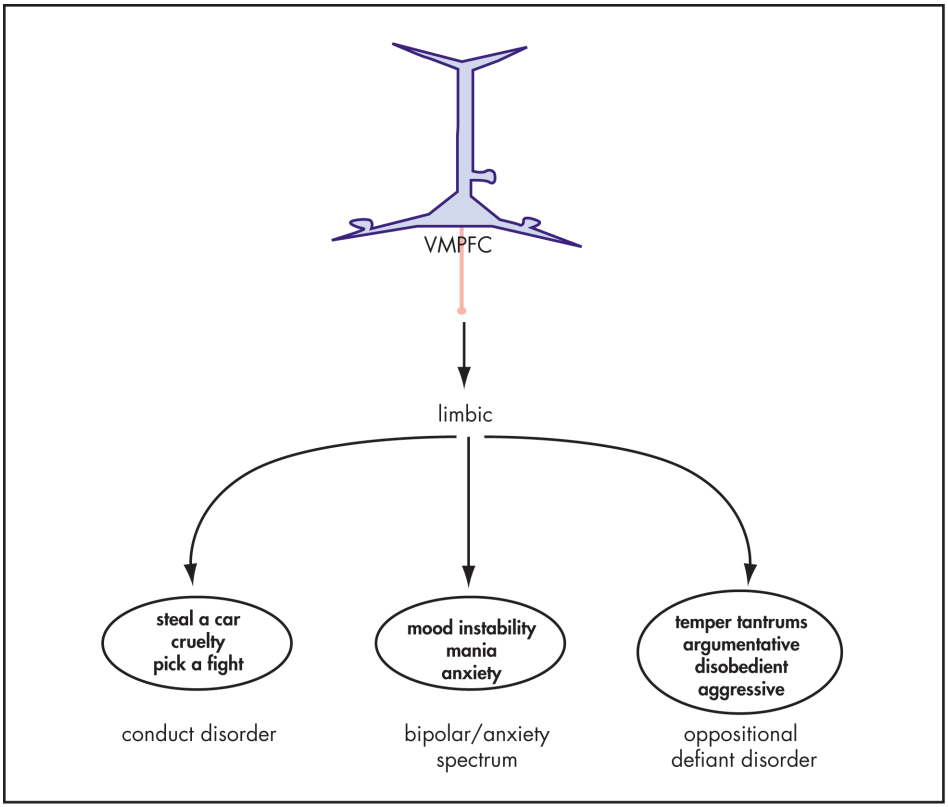

FIGURE 1.28. The comorbidities associated with ADHD are often the result of similar or additional dysfunctions within the prefrontal cortex-limbic network. As shown in Figures 3.2 and 3.3 many mood disorders are comorbid with ADHD both in children and in adults, and it has been suggested that the symptoms in adults might be most disabling if the comorbidities were already present in the child. This emphasizes the importance of treating all the symptoms in the younger population of ADHD patients in order to maximize their chances at a "regular" adult life.

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Similar Symptoms in Different Disorders:
Does It Matter?

Disorder / Symptom	ADHD	MDD/ GAD	Narcolepsy	OSA	SW	Sleep deprivation
Inattention/ problems concentrating	+++	++	++	++	++	+++
Mood/anxiety	-	+++	-	+	-	+/-
Sleepiness	+	+	+++	+++	+++	+++
Fatigue	+	++	++	++	++	+++

ADHD: attention deficit hyperactivity disorder; GAD: generalized anxiety disorder; MDD: major depressive disorder; OSA: obstructive sleep apnea; SW: shift work sleep disorder

TABLE 1.1. So, is inattention in ADHD any different from inattention in any other psychiatric disorder, and should it then be treated any differently? This is the question one can ask when examining the overlap of different symptoms in ADHD versus other disorders. The same brain circuits that mediate inattention in one disorder theoretically mediate inattention in other disorders (see first row in table above). Thus, treatments for inattention in one disorder may also be effective for treating inattention in another. The same holds true for mood/anxiety, sleepiness, and fatigue. Resolution of all symptoms, even if treated separately, may therefore lead to remission of the disorder.

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Impact of Genetics in ADHD

GENETICS	FUNCTION
DAT (dopamine transporter)	DAT clears DA from the synapse, transporting it back into the neuron
DRD 4 (D_4 receptor)	Member of the D2-like family of DA receptors; linked to G protein Gαi
DRD 5 (D_5 receptor)	Member of the D1-like family of DA receptors; linked to G protein Gαs
DBH (dopamine beta hydroxylase)	This enzyme converts DA to NE
ADRA 2A (alpha2A receptor)	Linked to G protein Gi, thus inactivating adenylyl cyclase
SNAP 25 (synaptic protein)	Synaptosome-associated protein of 25-kDa, inhibits presynaptic P/Q- and L-type voltage-gated calcium channels
5HTTLPR (long variant) (5HT transporter)	Serotonin-transporter-linked polymorphic region in this gene codes for different forms of the serotonin transporter
HTR 1B (serotonin 1B receptor)	Induces presynaptic inhibition in the CNS, and has vascular effects
FADS 2 (fatty acid desaturase 2)	Desaturase enzymes regulate unsaturation of fatty acids by adding double bonds between specific carbons of the fatty acyl chain

TABLE 1.2. Genetics play an important role in the etiology of ADHD. The mean heritability of ADHD is ~75%, making this disorder as heritable, if not more, as schizophrenia. As can be seen in this table, the major genes linked to ADHD are implicated in DA neurotransmission, with additional genes relating to adrenergic and serotonergic neurotransmission as well.

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SECTION 2:
Off the Beaten Path

As the pathophysiology of ADHD cannot yet be pinpointed to a specific event or cause, it is important to remain open-minded about how this disorder can be triggered in various people. Section 2 of Chapter 1 will look at off-the-beaten-path theories in the etiology of ADHD, some of which have very promising clinical data.

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Nature vs. Nurture

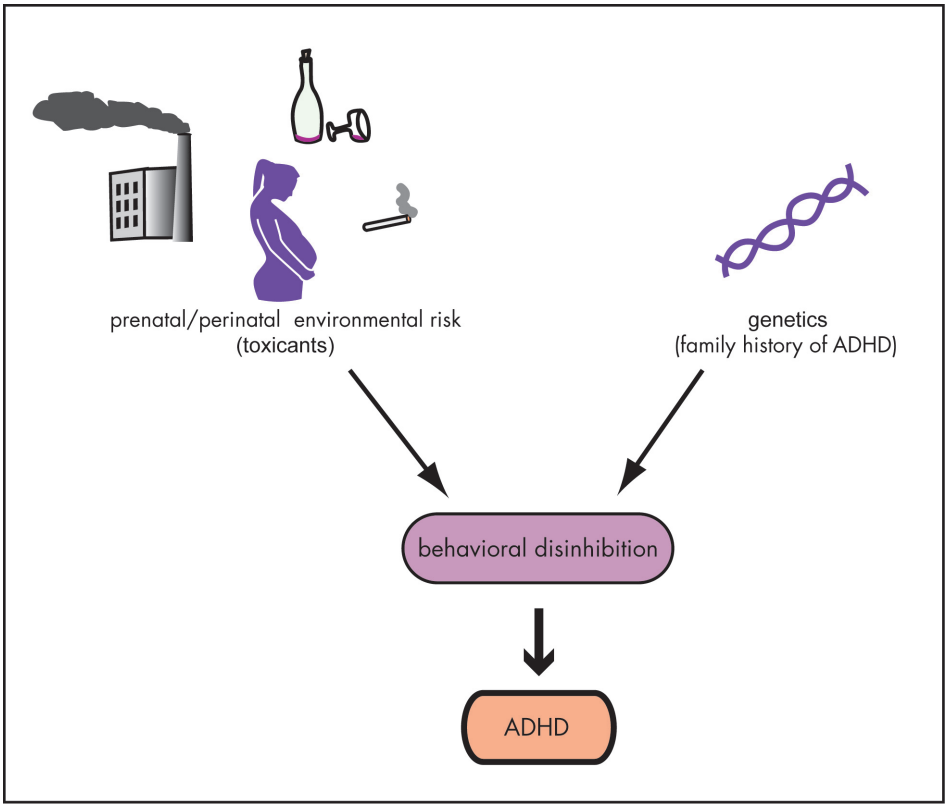

FIGURE 1.29. Theoretically the modern disease model of ADHD hypothesizes that different risk factors interact to lead to behavioral disinhibition and ultimately the symptoms of ADHD. Behavioral disinhibition, which is mainly a result of genetics, has been hypothesized to be at the core of ADHD. A certain combination of external risk factors such as prenatal tobacco and alcohol exposure, hypoxia, prematurity/low birth weight, emotional status of the mother during pregnancy, duration of labor, and low-level lead exposure can also impact the genetics of ADHD. Specifically it has been shown that children with hyperactivity often had more prenatal/perinatal complications.

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Iron Deficiency Hypothesis

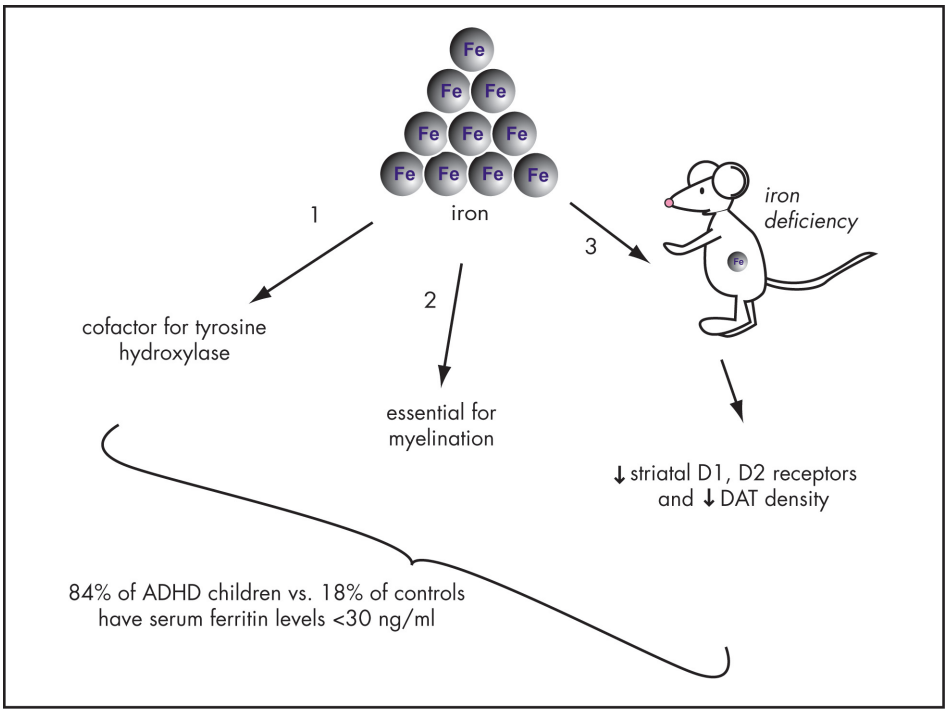

FIGURE 1.30. One of the newer theories in the etiology of ADHD implicates iron deficiency in the development of ADHD. Iron plays an important role in proper brain functioning and in DA neurotransmission. (1) Iron is critical in DA synthesis as it serves as a cofactor for tyrosine hydroxylase. (2) Iron is essential for myelination throughout the brain, a process needed to assure impulse speed along an axon. (3) In mice, iron deficiency can lead to reduced striatal D1 and D2 receptor levels as well as decreased DAT density, all of which will impact DA neurotransmission.

Clinical data also link iron deficiency to ADHD, with 84% of ADHD children, compared to 18% of control children, having serum ferritin levels of <30 ng/ml. It has been further hypothesized that iron deficiency could also be a factor in disorders comorbid with ADHD such as Tourette's syndrome and restless leg syndrome.

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Neuronal and Glial Energetics Hypothesis

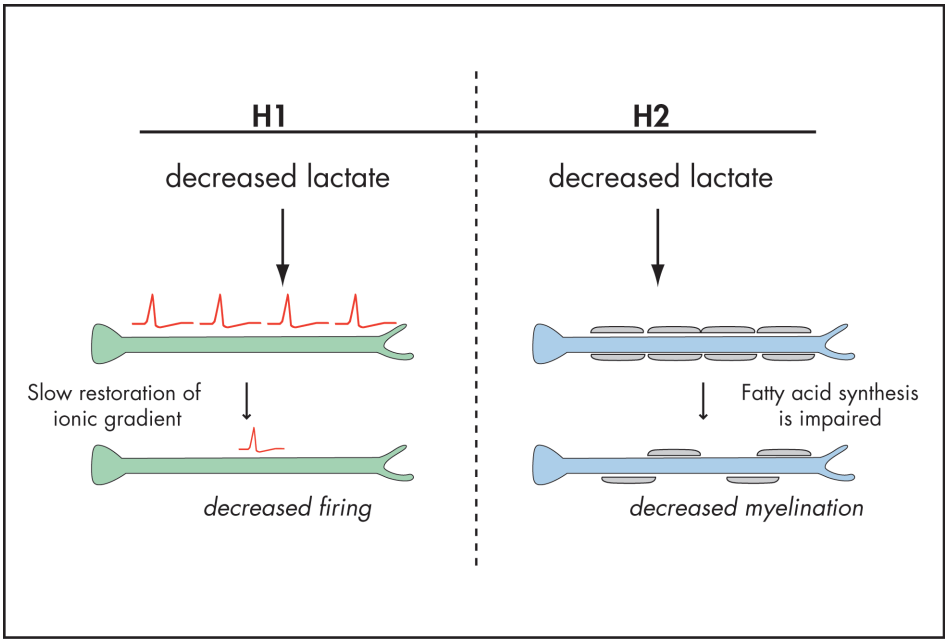

FIGURE 1.31. The neuronal and glial energetics hypothesis posits that astrocyte function is insufficient in ADHD thus leading to a deficit of lactate during brief periods of increased demands. Insufficient amounts of lactate will impair both performance (see Hypothesis 1) and development (see Hypothesis 2).

Hypothesis 1 (H1)—At the millisecond timescale: A lack in lactate will result in deficient amounts of adenosine triphosphate (ATP) in rapidly firing neurons. Consequently, ionic gradients will only be slowly restored, which will result in delayed neuronal firing, and thus a decrease in neuronal performance. Methylphenidate can, by stimulating glycolysis and lactate release from astrocytes, correct the energy deficiency thus leading to appropriate firing rates.

Hypothesis 2 (H2)—At the yearly timescale: Insufficient lactate supply in oligodendrocytes impairs fatty acid synthesis which leads to decreased myelination of axons during development. When axons are not properly myelinated this can result in slow transmission of action potentials, slow reaction times, and poor signal integration between brain regions.

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You Are What You Eat

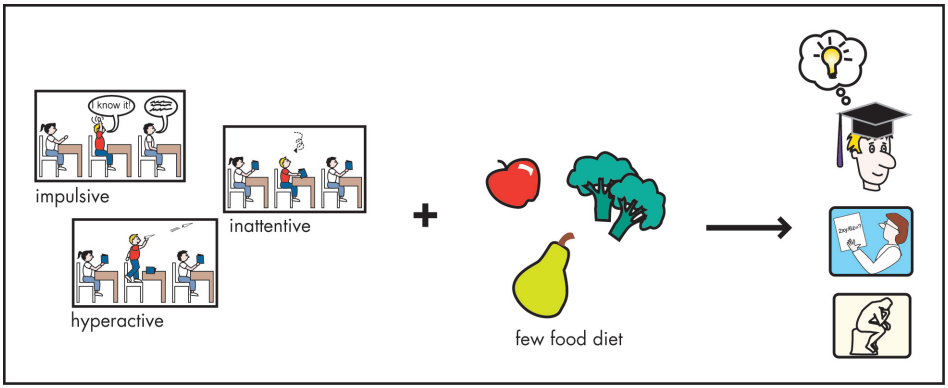

FIGURE 1.32. Another hypothesis put forth in the etiology of ADHD suggests that children with food sensitivities might react badly to certain foods and food additives. The underlying thought in this case is that, as sugar and food additives are chemical molecules, they may be able to induce brain changes—often negative ones. Various studies have looked at children with ADHD (as per DSM criteria) who were placed on a few food diet, which mainly consisted of fresh, non-processed food items. Up to 70% of the children responded very well to this new diet, and within nine weeks, they did not meet diagnostic criteria anymore as per the rating scales filled out by the parents and the teachers. While this approach might only be effective in a subset of children with ADHD it is worth investigating this issue further, as it can be initiated rapidly and reduces the reliance on pharmacological treatment.

In an additional placebo-controlled study where artificial foods were reintroduced and tastes hidden, it was shown that reintroduction of these sensitive foods led to reemergence of the ADHD symptoms, therefore implicating the food in the exteriorization of these behaviors.

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