Mechanism of Action of Stimulants in Attention-Deficit/Hyperactivity Disorder

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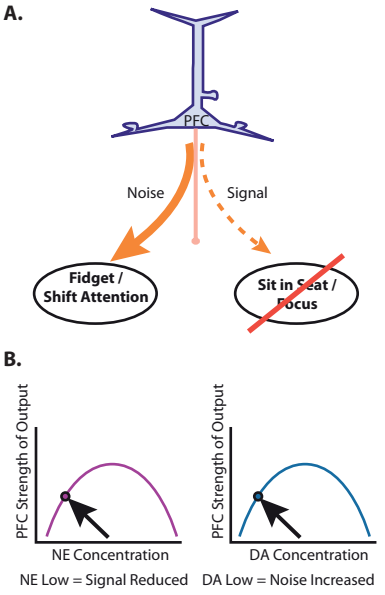
Issue: *Stimulants hypothetically increase the availability of both dopamine and norepinephrine in prefrontal cortex, which enhances the efficiency of information processing at pyramidal neurons, resulting in the improvement of symptoms in attention-deficit/hyperactivity disorder (ADHD).*

Take-Home Points

- Stimulants have long been known to increase dopamine (DA) in the prefrontal cortex (PFC).
- It is generally less well appreciated that stimulants also increase norepinephrine (NE).
- Symptoms of ADHD are theoretically linked to inefficient information processing by pyramidal neurons in PFC, perhaps due in part to imbalances in the neurotransmitters DA and NE.
- Stimulants such as methylphenidate and amphetamine hypothetically act at these pyramidal neurons to enhance signal strength by increasing NE and to reduce noise by increasing DA, thereby reducing symptoms of inattention, hyperactivity, and impulsivity in ADHD.

Figure 1. Classical Childhood-Onset ADHD



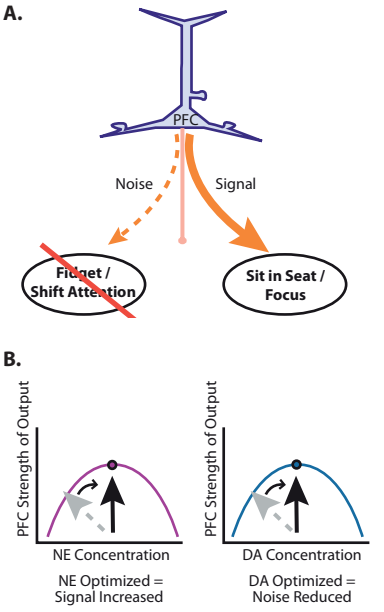
Hypothetically low signals and/or high noise in prefrontal cortex (PFC) due to low dopamine (DA) and/or low norepinephrine (NE)

A: In classical childhood-onset ADHD, the "noise" of irrelevant and extraneous inputs to the prefrontal cortex is hypothetically too high to be ignored, whereas the "signals" to which a person needs to pay attention are too low to be noticed.[1–4]

B: DA acts to block noise, while NE serves to enhance signals. In patients with ADHD, DA and/or NE are hypothetically low, analogous to a guitar string that is too loose, thus being "out of tune," which may be linked in part to deficiencies in the actions of both DA and NE at pyramidal neurons,[1–4] resulting in high noise and low signals.

Behaviorally, this situation can translate into a child with hyperactivity, impulsivity, and inattention or an adult with mostly symptoms of inattention.

Figure 2. ADHD Treatment With Stimulants



Increase NE and DA in PFC

A: To treat the symptoms of ADHD and thus reduce hyperactivity and impulsivity, while enhancing attention and focus, treatment with stimulants will theoretically increase signal strength by dialing up NE actions and reduce noise by dialing up DA actions.[1–4]

B: Generally, information processing in pyramidal neurons can be described as an inverted U-shaped curve.[3–8] Low signals can be enhanced by NE, and high noise can be reduced by DA.[5–8]

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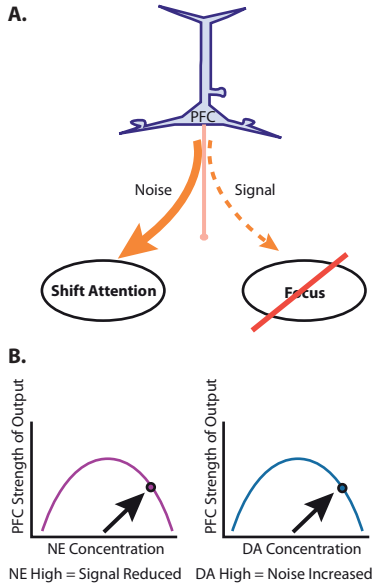
Figure 3. ADHD and Acute Stress



Hypothetically low signals and/or high noise in PFC due to high DA and/or high NE

A: Stress can lead to abnormalities of information processing in PFC and to symptoms of ADHD, particularly inattention.[3,4]

B: In contrast to the case for classical ADHD, however, here NE and DA levels may be too high, analogous to a guitar string that is too tight, thus, still out of tune, yet information processing is just as compromised as when NE and DA levels are too low (see Figure 1B).[3,4] The imbalance is theoretically due to the nature of information processing by pyramidal neurons in PFC, which are regulated by DA and NE.[3–8]

This situation can be mistaken for the symptoms of ADHD, particularly in adults, and in this case stimulants may either not work or make the situation worse by raising DA and NE even more.[2,3] Physicians need to be aware of this potential reaction in some patients.

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From the Neuroscience Education Institute in Carlsbad, California, the Department of Psychiatry at the University of California San Diego, and the Department of Psychiatry at the University of Cambridge, Cambridge, United Kingdom.

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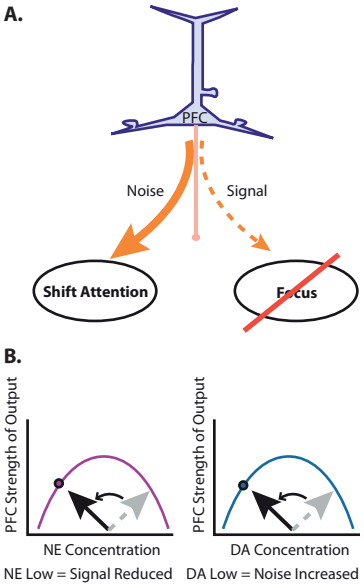
doi:10.4088/JCP.09bs05890pur

Figure 4. ADHD and Chronic Stress



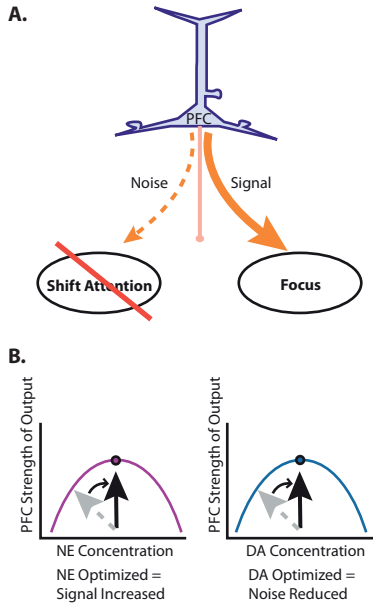
NE and DA depletion over time

A: Excessive activation of NE and DA in PFC over time due to chronic stress can lead to depletion of NE and DA and to a situation similar to classical ADHD in terms of symptoms.

B: Chronic stress can lead to a similar effect on PFC NE and DA concentrations (cf Figure 1A and B).

Adults with comorbid ADHD plus chronic stress can lead not only to a worsening of ADHD, but to the frequent presence of comorbid stress-related conditions, especially anxiety and substance abuse.[3,4]

Figure 5. Stimulant Treatment for ADHD and Comorbid Chronic Stress



Reestablish NE and DA in PFC

A: To treat the symptoms of ADHD, especially in adults with comorbid chronic stress and symptoms of inattentiveness, stimulants may be given to increase depleted NE and DA (cf Figure 2A and B).

B: Stimulants increase NE and DA and improve concentration (see 5A).[3,4] In addition, stimulants can improve the symptoms of stress-related conditions, such as comorbid anxiety and substance abuse.[3,4]

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