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Shifting Focus: From Group Patterns to Individual Neurobiological Differences in Attention-Deficit/Hyperactivity Disorder

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Henry has earned a reputation as the “troublemaker” of his first-grade class. Throughout the day he speaks over others, squirms in his seat, climbs on furniture, and does not listen.

Eli is a quiet fifth grader who is falling behind. While he is smart, he appears distracted and cannot organize himself to complete increasingly complicated assignments.

Courtney completes her third-grade assignments slowly and makes careless mistakes. She recently hit a classmate who mocked her for walking around during reading time. She tantrums when starting homework, and her mother's attempts to bribe her with a future ice cream reward are unsuccessful.

Henry, Eli, and Courtney's parents have many concerns. Will Henry grow out of this? Why is Eli suddenly falling behind? Is Courtney a bad child?

Despite the differences in the way these children present, all of them are eventually diagnosed with attention-deficit/ hyperactivity disorder (ADHD). ADHD is characterized by a pattern of inattention and/or hyperactivity-impulsivity that is developmentally inappropriate and impairs functioning. Problems are often first noticed in school, but the diagnosis requires symptoms in at least two settings for at least 6 months. ADHD is a clinical diagnosis requiring anywhere between 6 and 18 symptoms from “inattentive” and/or “hyperactive-impulsive” categories in the DSM-5, making it a catchall diagnosis encompassing a wide variety of clinical presentations. The vignettes above demonstrate that different individuals may present with symptoms primarily reflecting hyperactivity (Henry), inattention and executive functioning difficulties (Eli), or a combination of both (Courtney).

ADHD is common, with an estimated worldwide prevalence of around 7.2% for children under 18 years of age (1). It has a genetic component and often presents with comorbid disorders, such as oppositional defiant disorder and anxiety (2), contributing to further individual differences in presentation. Many children diagnosed with ADHD will not meet full criteria for the disorder as adults but can continue to have symptoms that impact their

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personal and professional lives. With such heterogeneity in presentation and trajectory of illness, it is difficult to conceptualize ADHD as one consistent entity. Do Henry, Eli, and Courtney really have the same disorder?

Despite being a common disorder, the underlying neurobiology of ADHD is not fully understood. Early research focused on the role of dopamine and its transporter (3), because stimulants modulating the dopaminergic system have been a relatively effective mainstay of treatment since the 1950s. However, like most other psychiatric disorders, there is now evidence of dysregulation in multiple neurotransmitter systems. With the advancement of neuroimaging, research has shifted into identifying structural and functional differences in ADHD. Just as no individual neurotransmitter can explain the disorder, no discrete brain structures can explain the picture, and studies have yielded inconsistent findings. Some of these inconsistencies may reflect the heterogeneity of ADHD afforded by the current method of diagnosis.

Symptoms of ADHD are thought to be related to differences in functional connections between multiple complex brain systems, as well as structural differences, such as lower gray matter volume in certain regions that may normalize with age (4). Multiple systems may be implicated in each cognitive domain.

Attention networks are commonly involved in ADHD, and symptoms of inattention can include difficulty focusing, making careless mistakes, and appearing to not listen. Neuroimaging studies performed during attentional tasks in those with ADHD demonstrate several functional differences. For example, there may be lower activation in the links between the frontal and parietal cortices, showing that the appropriate directing of attention during goal-oriented tasks may be impaired (5). Children with ADHD may have lower activation of the ventral attention network (consisting of the temporoparietal junction and ventral frontal cortex), which is important in responding to unexpected but relevant stimuli (5). The default mode network, a system of many interconnected regions, including the medial prefrontal cortex, posterior cingulate cortex, medial temporal lobe, and lateral parietal cortex, is also involved in ADHD. This system is inactive when one focuses on external cues and active when one is at rest and occupied by internal cues. In ADHD there is altered connectivity and less resting anticorrelation of the default mode network with systems involved in external focus— meaning those with ADHD can have difficulty dividing attentional resources between internal and external cues (6).

Another core system thought to be involved is the reward network, which is composed of the ventromedial prefrontal cortex, orbitofrontal cortex, striatum, anterior cingulate cortex, and amygdala. Those with ADHD prefer immediate to delayed rewards and show differences in the anticipation and processing of rewards. Children with ADHD may have difficulty with real-life “marshmallow tests,” such as waiting their turn, and adolescents with ADHD may be prone to engage in more impulsive reward-seeking behavior. Functional neuroimaging has demonstrated that adolescents and adults with ADHD demonstrate lower activation of the ventral striatum during anticipation of rewards, possibly making delayed rewards less desirable (7). Neuroimaging studies examining differences in immediate and delayed reward processing have been less consistent but suggest that there are functional differences.

While diagnostic criteria are currently categorized under the label of “inattention,” it may be more parsimonious to think of those symptoms as reflecting deficits of executive function — including planning and organizing, performing complex tasks, and inhibitory control. More complicated cognitive tasks tend to involve frontal brain regions, such as the prefrontal cortex and connections to the parietal cortex. Without planning and inhibitory control, children with ADHD can act impulsively and have difficulty getting started with complicated tasks. Children can present with difficulties as they advance through school and work becomes more demanding. The executive control network and corticocerebellar networks often interact with each other to help perform many executive functioning tasks and consist of several structures with some overlap, including the frontal cortex, basal ganglia, dorsal anterior cingulate cortex, and cerebellum. These networks may demonstrate less connectivity and lower levels of activation during executive function tasks in ADHD (5).

Taken together, these common cognitive symptoms of ADHD may involve differences in the structure and function of frontal-striatal-parietal-cerebellar pathways (Figure 1). There are relatively few neuroimaging studies examining the motor systems in ADHD, but early research has suggested hypofrontality during motor control tasks in children with ADHD (8).

Given its heterogeneity, combining the neuroimaging data of ADHD inherently presents a group to individual problem, wherein data obtained from group averages may not accurately reflect what is occurring in any particular individual—that is to say, different children may have different underlying processes at play (9). Further complicating this is the unclear impact of comorbidities on neuroanatomical differences seen in ADHD (10). In their neuroimaging study addressing this question, Noordermeer et al. (10) showed that a group of participants with ADHD/oppositional defiant disorder had greater volumetric reductions in frontal regions than an ADHD-only group. They therefore suggested that the overlap of affected regions between commonly comorbid disorders may create a structural “double burden” in those areas. Children with comorbid oppositional defiant disorder are often included in ADHD neuroimaging studies, which may skew averages and exacerbate the group to individual problem.

Rather than thinking of ADHD as one entity, it may be helpful to conceptualize the various presentations of ADHD as having unique differences in neurobiological pathways thought to underlie the symptoms. Though we currently lack the tools to diagnose and make recommendations at the neurobiological level, this concept of ADHD as multiple distinct entities may help physicians understand differences in presentation. Individual differences in treatment response are also likely related to comorbidities, specific sets of ADHD symptoms, and their corresponding affected brain pathways. Additional research may promote the future possibility of diagnosis and treatment based on individual symptom profiles.

How would this help when a child is sitting in front of you? One may begin to understand that Henry is not just another child with ADHD—he is someone with differences primarily in brain systems involved in inhibitory and motor control and may have difficulty maintaining friends because of this dysregulation. Scheduled breaks and a daily chart where

he earns stickers for staying in his seat may help him better manage his behavior. Eli might feel frustrated with his new difficulties because his intelligence may have previously masked underlying differences in attention and systems involved in planning and organization when schoolwork was easier. He may benefit from extra time on tests, preferential seating, and creating checklists. Differences in Courtney's reward processing system, inhibitory and motor control systems, and attention networks may make it difficult for her to process and appropriately deal with stimuli and she may receive frequent punishments. However, Courtney's treatments may involve training parents and teachers to praise specific correct behaviors as soon as they occur.

Parents of children with ADHD may already feel stigmatized because of their child's behavior and may have reservations about seeking psychiatric care. Proper treatment of ADHD is imperative to a child's social, emotional, and academic development. As physicians, it is important to send the message to parents that children like Henry, Eli, and Courtney are not "bad children." Instead, they have alterations in certain brain pathways involved in attention and/or hyperactivity-impulsivity and can all do well with treatment focused on their individual needs.

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Figure 1. Areas of structural overlap in regions thought to be related to reward, attention, and executive functioning differences in attention-deficit/ hyperactivity disorder. Areas with more overlap include the frontal cortex, striatum, and parietal cortex. Symptoms of attention-deficit/hyperactivity disorder are related to differences in functional connectivity between multiple complex neurobiological systems.