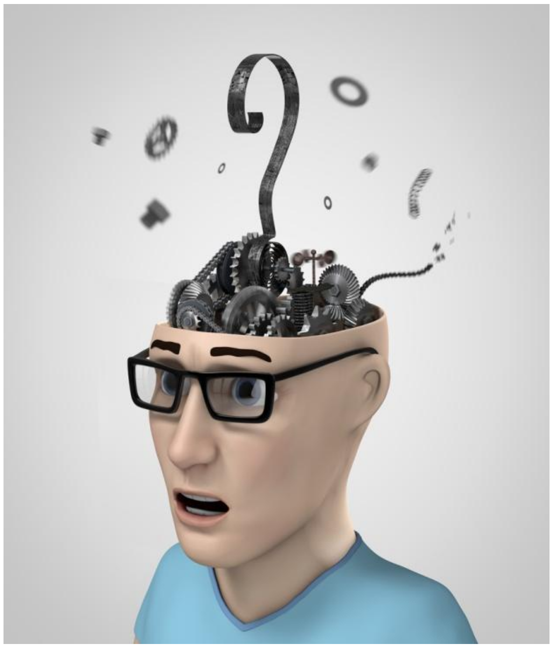
ADHD: 10 Years Later

By Philip Shaw



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Editor's Note: Estimates of children struggling with attention-deficit/hyperactivity disorder (ADHD) vary, but the Center for Disease Control puts the number at a stunningly high 25 percent. Whatever the number, ADHD affects too many children at school, at home, with their peers, and often persists into adulthood. The cause is as yet unknown, although genetic factors and their interaction with the environment are known to be pivotal. Ten years ago a landmark study showed that the structure of the brains of children with ADHD differs from that of unaffected children. Since that study, enhancements in imaging have given researchers a better look at key hubs in the brain and how they network—advances that could prove useful in the control and treatment of ADHD in both children and adults.

Imagine two children, both eight years of age, sitting in science class. Both focus on the chalkboard and the teacher as she explains why Earth orbits the sun. The first child, Toby, is engrossed in the topic; he gazes intently at the teacher and at diagrams of the solar system. The second child, Susan, tries to stay focused but keeps getting distracted, first by the whispering of a classmate, then by the sunny day outside, and finally, by the antics of the classroom hamster. She fidgets constantly and is frequently out of her chair, despite the teacher's reminders to stay seated.

What brain events underpin the different behaviors in these two children? Think first of Susan's fidgeting. This apparently simple movement is not the result of one isolated part of the brain. Rather, it's the result of a network of brain structures acting in concert to produce movement. These networks are made up of key components, or hubs, that are connected by specialized links known as white matter tracts. In the planning and execution of movements, the key hubs include parts of the prefrontal cortex (the motor and premotor cortex) and deeper brain structures.[4, 19, 20] The deeper structures include the putamen, the thalamus, and the cerebellum. The putamen, thalamus, and cerebellum add and integrate relevant information, which is then relayed back to the cortex.

Now consider each child's ability to stay focused on the teacher and directed toward the goal of learning. This ability also depends on brain structures that act together. In this case, the network is responsible for controlling a highly complex cognitive act, which it achieves partly by integrating information from the lateral prefrontal and parietal cortices. Often this information is further relayed through deeper structures in order to guide behavior, to make decisions, and to solve problems. Considering all of the brain activity necessary to stay focused in the classroom, it is easy to see how problems with these networks could translate into challenges with attention and motor control.

Problems with the control of attention, impulses, and movement can be severe. In the extreme, they are strongly associated with a child struggling academically at school, sometimes having difficulty forming friendships with peers, and causing problems at home.[8, 11, 30] Such problems can prompt a full clinical assessment, which generally involves talking with parents and teachers. The result may lead to a diagnosis of attention-deficit/hyperactivity disorder (ADHD).

How has imaging of the structure of the brain added to the understanding of problems in the domains of attention, impulse, and motor control—the cardinal features of ADHD? Three points emerge. First, key regions or hubs in the networks mediating the control of attention and action sometimes show structural differences between groups with and without ADHD. Second, the hubs' physical connections, formed by white matter tracts, may also differ in the brains of people with impaired attention. Finally, some of the structural differences associated with ADHD are not fixed and static, but rather change as a child grows.

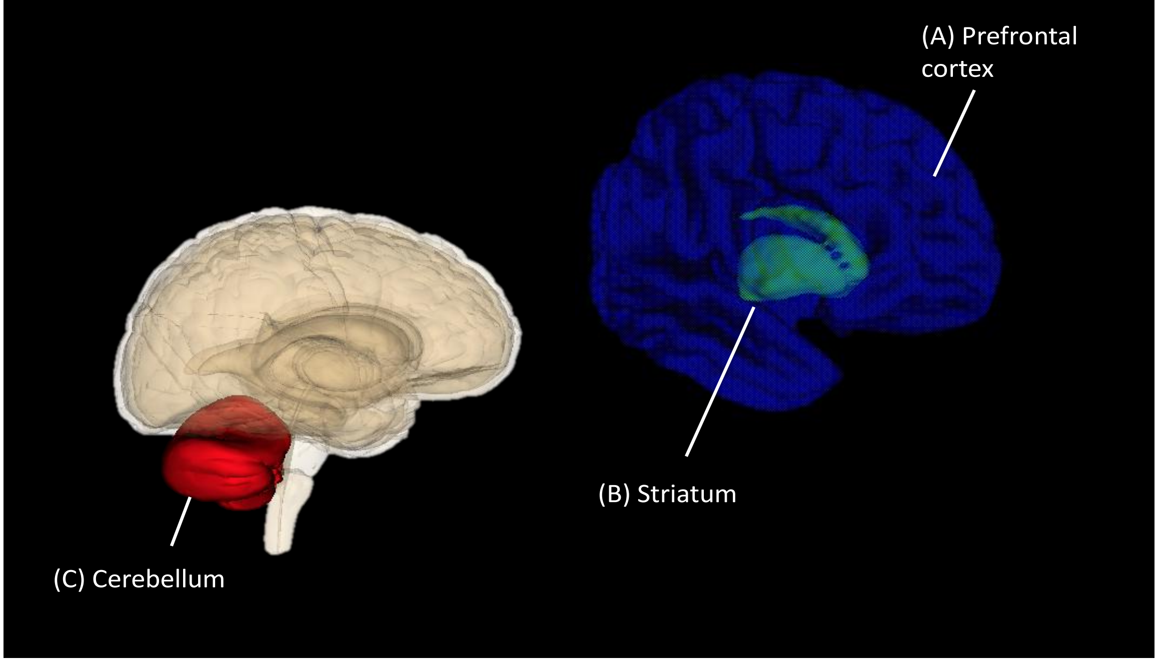
What Do We Know?

What has brain imaging found? Just over 10 years ago, a landmark study used anatomic MRI to compare 152 children with ADHD to a group of 139 children with no symptoms. The

ADHD group showed a slight reduction—about 3 percent—in total brain volume.[5] This did not mean the children with ADHD were less intelligent; they were as intelligent as the comparison children in the study. Rather, it suggested that severe, impairing problems with attention, impulse, and activity control are associated with differences in brain structure.

Since this study, marked advances in acquiring and analyzing brain images have enabled researchers to pinpoint the brain regions most tightly linked with ADHD. These advances allow the identification of structural differences in the hubs of networks that most strongly contribute to challenges with control of attention and movement. Three hubs are shown in the figure (see below). Many studies have defined brain-volume change in terms of voxels.

Figure: The key components or 'hubs' of the networks that support the control of action and attention are shown. These include (A) regions of the prefrontal cortex (particularly the dorsolateral cortex, and the midline cingulate cortex, which is not shown); (B) parts of the striatum; (C) the cerebellum, particularly the midline vermis. These regions are interconnected.



When we pool the results of these studies, the aggregate findings point to key hubs that might be important in the control of attention. The first candidate hub lies in the striatum, a deep brain structure made up of two substructures, the caudate and the putamen. The striatum, which lies near the center of each hemisphere, interacts richly with multiple other brain regions. It is a hub in networks supporting many cognitive skills, such as the flexible control of attention and motor planning. The striatum is slightly smaller in groups with ADHD compared to those without. The effect is more prominent on the right side of the putamen and the anterior parts of the caudate. Many individuals with ADHD find attention-control and motor-planning skills particularly challenging. It thus makes perfect sense that this region would show structural change. More recent work suggests that changes to the striatum apply not only to its volume, but also to its surface contours, with reports of "indentation" in parts of the striatum in groups with ADHD.[26] At an even deeper level in the striatum, images show changes in the density of receptors for dopamine, which is one of the chemicals in the brain that is important in communication between cells.[29]

A second set of candidate hubs has been localized to the prefrontal cortex. This set emerged partly from studies that mapped both cortical thickness and surface area at thousands of points across the brain. Most of these studies indicate that the dorsolateral prefrontal cortex is slightly thinner in groups with ADHD compared to those without the condition.[1, 2, 17, 23] This frontal region is a central hub in the networks controlling the most complex executive functions, such as allocation of attention, planning, and decision-making. A second structurally altered hub lies in the cingulate cortex, which is pivotal in monitoring the environment and adjusting behavior in response to feedback. Tellingly, both of these frontal areas belong to networks that include parts of the striatum.

A child's environment has an exquisite temporal structure; successful navigation requires the ability to process information that changes extremely quickly—on the order of milliseconds. [6, 18, 21, 22, 25, 27] For example, a conversation requires the ability to judge exactly when someone is about to stop speaking and then to respond within an appropriate time period. A child may appear impulsive because they fail to judge exactly the correct amount of time needed before responding to a teacher, for example, and interrupt. The cerebellum is a critical part of the networks responsible for such temporal information processing. Decreased volume of the cerebellum has been found in groups with ADHD, compared to groups without ADHD.[3, 16] The midline section of the cerebellum—called the vermis—has been most strongly linked with attention problems. Notably, the vermis is richly interconnected with the cortical hubs mentioned earlier.

In short, a series of networks controls attention and action. Within these networks, three hubs emerge as important: centers in the prefrontal cortex, the striatum, and the cerebellum. This concept of networks provides hope for overcoming attention problems. For example, one hub might be able to compensate for another, a point we will return to later.

MRI as a Game Changer

Magnetic resonance imaging (MRI) allows us to look at the brain. It leverages the fact that different tissues and regions can produce a different “signal” when placed in a strong magnetic field. This approach is safe, as it does not use ionizing radiation. Just two of its many applications are considered in this article. The first is the physical definition of the brain’s various structures. Scientists once established these boundaries by tracing around entire structures with their hands, but over time they have increasingly used objective computational approaches to define structures at a much finer level of resolution. For example, in one approach, scientists divide the brain into hundreds of thousands of tiny boxes, or voxels (mentioned earlier), and measure the volume of each voxel. In another, they look at the thickness of the cortex at hundreds of thousands of points across the brain. Both approaches afford exquisite precision in mapping anatomical differences.

The second relevant application of MRI helps scientists define the brain’s “wiring.” White matter tracts, which often connect different brain regions, have physical properties that can be measured by MRI. Water molecules in the brain move randomly unless they are constrained by a physical barrier. White matter tracts, or, more precisely, the myelin sheaths that form tracts, are one such barrier. These tracts can be mapped using a form of MRI called diffusion tensor imaging (DTI), which enables us to better understand the connections between brain regions.

When describing the findings, it is important to stress that the brain-structure differences emerge from studies that compare one group with ADHD against a group without it. On average, the size of certain brain structures differs between these groups. However, the size of brain structures varies greatly within both groups, and the size of brain structures also overlaps significantly between the groups. For example, the volume of a structure called the striatum is lower, on average, in groups of people who have ADHD than it is in groups of people who do not have ADHD. This means that the distribution (or the spread) of striatal volumes in ADHD is shifted, compared to the distribution of areas in the comparison or control group. There is, however, still much overlap between the distributions. In other words, the volume of an individual's striatum is insufficient information for a diagnosis; the diagnosis is still based on a careful assessment that includes feedback from family members and teachers. Nonetheless, the robust group differences found in neuroimaging studies gives us invaluable insights into the neurobiology of inattention, impulsivity, and hyperactivity. Researchers are benefiting from the emerging picture of group-level structural change in brain regions that are pivotal in the cognitive processes most affected in ADHD. Such work not only guides research, but also may inform future treatment.

The Brain's Wiring

A good network requires good communication. Carrying information quickly and efficiently between hubs in a network is a prerequisite for optimal brain functioning. Using techniques such as DTI, we can map the brain's communication pathways. Scientists debate about the exact physical properties that DTI captures, but broadly speaking, one measure—the fractional anisotropy—reflects the structural integrity and organization of white matter tracts. Some themes emerge when we pool the results of DTI studies comparing groups of individuals with and without ADHD. [13, 28] First, fractional anisotropy is lower in some regions of the brain in groups with ADHD compared to groups without the condition. These changes are prominent, but they are not confined to the tracts that link the hubs mentioned earlier. To give a specific example, reduction in fractional anisotropy localizes to a region near the tracts that connect the cerebellum with prefrontal cortical hubs important for motor control. Another region that shows change contains the white matter tracts that connect different cortical hubs (the superior longitudinal fasciculus).

Accelerating the development of new methods to map brain structural connectivity is the Human Connectome Project, a five-year project sponsored by sixteen components of the National Institutes of Health and split between two consortia of research institutions. The project is the first large-scale attempt to collect and share data of a scope and level of detail sufficient to begin the process of addressing fundamental questions about human connectional anatomy and variation, with the hope of gaining a richer understanding of the connectivity problems that underpin challenges in attention and impulse control.

Cause or Effect?

Are these brain structural changes the result, rather than the cause, of problems with inattention, impulsivity, and hyperactivity? Evidence from studies on families indicates that brain anatomic changes are not merely the result of having symptoms of ADHD, but rather they are a causative factor. In these studies, siblings with and without ADHD are compared. The studies indicate that changes in brain structures in unaffected siblings that resemble the structural changes in siblings with ADHD cannot be due to ADHD symptoms, as the unaffected siblings have no symptoms. Rather, the brain changes reflect familial, likely genetic, influences on brain anatomy. One study demonstrated that children with ADHD and their unaffected siblings share similar structural brain differences, including a slight reduction in the volume of the prefrontal cortex.[9] Another study found white matter tract structure changes in both individuals with ADHD and siblings without ADHD.[15]

Similar family studies have long been used to isolate genes that contribute to mental-health problems. An exciting future direction is to adopt this approach in neuroimaging by identifying the brain changes that track attention problems within families. Such work is particularly compelling given the possibility of sequencing the genome—that is, spelling out the entire genetic code of an individual. Harnessing the power of both genomic sequencing and rapidly advancing neuroimaging techniques will yield great insights into the mechanisms underpinning the control of attention and action and why they sometimes go awry.

The Dynamic, Developing Brain

Think back to Susan, the child whose problem with staying focused was impacting her ability to learn. How do children with problems similar to Susan's fare as they grow up? Several large studies follow children with a diagnosis of ADHD into adulthood.[24] Full-blown ADHD persists around 20 percent of the time. While a further 50 percent have symptoms that impair day-to-day living, they do not have enough symptoms to warrant a formal diagnosis. The remainder shows more robust improvement, with resolution of most symptoms. Generally, hyperactivity and impulsivity tend to improve more than inattention does. As with many challenges of childhood, ADHD has a highly variable course. Understanding the brain changes or trajectories that underpin these variables could help us devise treatments to keep brain development on track.

Longitudinal data can be particularly powerful in defining these trajectories. In one study, children with ADHD underwent repeated assessment of their symptoms along with MRIs as they grew into adulthood.[24] This approach allowed researchers to link the trajectories of brain development with adult outcomes. Some differences in trajectories emerged in a prefrontal cortical region mentioned earlier: the cingulate cortex. This region is a key hub in a network that keeps an individual on task and monitors the environment for relevant information.[19] In the study, individuals whose attention improved started with a thinner cortex in childhood, but the cortex eventually grew to the same thickness as a comparison group that never had ADHD. By contrast, those who had persistent inattention into adulthood did not show this convergence; rather, their cortices showed a fixed difference. There was a great deal of variability in these trajectories, but overall differences in the development of an "attention hub" were associated with later outcome. Movies provide more information than snapshots do: likewise, developmental differences important for the control of action and attention can often be captured better by longitudinal than cross-sectional data.[14]

Developmental Perspective

Thinking of the brain as a developing network might inspire new approaches to help people overcome impairing problems with attention and impulsivity. Perhaps intact hubs in a network can be recruited to compensate for suboptimal performance of other networks.[7]

Or perhaps through techniques such as cognitive-skill training, people with ADHD can improve communication between key hubs.[12] Our emphasis on the importance of taking a developmental perspective underscores the brain's capacity for beneficial change. It is exciting to think how the enormous potential for brain plasticity in childhood and adulthood could be harnessed to improve attention skills and to boost motor and cognitive control.

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