Approaching a Scientific Understanding of What Happens in the Brain in AD/HD

by Xavier Castellanos, M.D.

Thirty years ago, a revolution in psychiatric perspectives was launched with the birth of clinical neuroscience and neuropharmacology, loosening the grip of the empirically unverified psychoanalytic theories that held sway in psychiatry for half a century. By 1980, with the publication of the Diagnostic and Statistical Manual - Third Edition, psychiatry shifted toward a syndrome-based diagnostic system, one that did not rely on unproven theories, but rather, specific, observable criteria as the bases for making reliable diagnoses. Coincidentally, the availability of neuroimaging techniques has, for the first time, allowed practical access to the living human brain. It is now possible to propose theoretical models of how the brain works in individuals who have identifiable disorders, such as attention-deficit/hyperactivity disorder (AD/HD).

These models of brain function, while necessarily simplistic - they gloss over almost all of the immense complexity of the brain - can nonetheless help continue the momentum toward a scientific understanding of normal and abnormal brain functioning, and to further honing and improving of treatments and interventions for specific disorders. I have attempted to formulate such a model of AD/HD based on clinical and basic science observations.

The model described here is limited to central dopaminergic systems (dopamine is a neurotransmitter, or messenger molecule, that traverses the synapses in the brain, allowing one neuron to communicate with the next in the chain) and how they regulate circuits in the most anterior region of the brain (termed the prefrontal brain).

Current Research Conclusions

Most studies of AD/HD have not pursued the development of brain models. Rather, studies over the past two decades have sought to better characterize AD/HD, primarily in children. Based on an admittedly selective reading of this voluminous literature, the following conclusions can be reached:

AD/HD is a common although highly varied condition. One element of this heterogeneity is the frequent co-occurrence of other conditions (comorbidity). "Pure" AD/HD may be best characterized as a risk factor for other psychiatric and psychosocial problems such as oppositional defiant disorder, conduct disorder, and substance abuse. "Pure" AD/HD does imply a somewhat negative prognosis, but this is magnified greatly by the presence of other comorbid conditions.

AD/HD is a developmentally sensitive disorder, representing, at least in part, a "neurodevelopmental lag." Impairment associated with AD/HD symptoms can continue throughout life, although the specific symptoms and spheres of functioning that they affect often change. The risk of serious negative consequences from AD/HD and associated conditions is highest during adolescence.
Neither specific deficits in attention nor in motor control are adequate to explain the range and variety of AD/HD symptoms.
The psychological construct of "executive functions" provides a useful unifying framework from which to describe AD/HD symptoms throughout life.
The brain circuits that serve executive functions include the prefrontal cortex (the outer layer of gray matter covering the cerebral hemispheres), the basal ganglia (four collections of neurons located deep in the cerebral hemispheres), and the cerebellum (a portion of the brain involved in the control and coordination of skeletal muscles for voluntary movements; it does not initiate movements but does interact with many brain stem structures in executing a variety of movements, including walking, running, and fine voluntary movements as required in writing, dressing, and eating). These circuits are modulated by many neurotransmitters, including dopamine.
Drafting a model of AD/HD requires understanding normal brain development, the most dramatic feature of which is a relative increase of inhibiting messages compared to excitatory, "impulsive" messages with increasing maturation. This maturing is paralleled by decreases in dopamine concentrations in the brain.
Dopamine concentrations are greatest in the most hyperactive boys with AD/HD, consistent with the "neurodevelopmental lag" theory.
Prefrontal circuits, particularly in the right hemisphere, have been implicated in AD/HD by neuroimaging studies.
Delayed maturing of prefrontal circuits into the third decade of life is consistent with the improving prognosis for most adults with AD/HD.
Treatment strategies for AD/HD must be grounded in a developmental perspective.

The Developmental Course of AD/HD

As a disorder identified primarily with pediatric patients, it is not surprising that AD/HD raises several developmental issues. First, a number of observations support the conclusion that AD/HD represents, at least in part, a "neurodevelopmental lag" (Kinsbourne, 1973). For example, children with AD/HD trail about two years behind peers of the same age in social development (Dykens et al., 1990). A similar gap of two to three years was found in cognitive tests believed to tap prefrontal functions in eight and nine-year-olds, and ten to twelve-year-olds (Chelune, et al., 1986; Armin, et al., 1993). Thus, children with AD/HD and those who do not have the disorder seemed to be progressing at the same rate but with a relatively constant lag of two to three years.

Second, the symptoms of AD/HD change over time. The most obvious characteristic of the young child with AD/HD is motor hyperactivity, which decreases over time even if no treatment is provided (Frick, et al., 1994; Hart, et al., 1995). By contrast, symptoms of inattention show little improvement over time. In fact, it is not uncommon for symptoms

of inattention to be difficult to discern in the elementary grades, only to become more noticeable as the complexity of academic challenges increases.

Executive Functions and the Neuropsychology of AD/HD

Neuropsychological approaches have been employed in an attempt to isolate the cognitive deficit or deficits underlying AD/HD so as to improve diagnosis and implement more targeted treatments.

The search for neuropsychological deficits that would correspond to the symptoms of AD/HD has come to focus on the concept of executive functions. Executive functions have been defined as "control processes' [involving] inhibition and delay of responding [allowing an individual to] initiate, sustain, inhibit/stop, and shift" (Denckla, 1996). Also associated with executive functions are the abilities to prioritize, organize, and strategize (Denckla, 1989).
Executive dysfunctions are clearly present in patients who have AD/HD. The similarities between patients who have AD/HD and those who have frank lesions of the prefrontal brain have long been noted, but so too have the limitations of this crude comparison (Pontius, 1973; Benton, 1991; Mattes, 1980). Over the past decade, however, a more nuanced understanding of the brain circuits that serve frontal functioning has emerged (Alexander, et al., 1986; Alexander & Crutcher, 1990).

The Brain's Braking System

In order to discuss the brain's "braking system" we need to define some terms:

Neuron: A nerve cell, the structural and functional unit of the nervous system.

Axon: The long, tube-like part of a neuron that extends to the next neuron in the pathway.

Synapse: The place where two neurons in a neural pathway communicate; an impulse traveling along the axon in the first neuron releases chemicals (neurotransmitters) when it reaches the synapse which "unlock" impulses in the second neuron.

Gray matter: Collections of neuronal cell bodies, where incoming signals are processed.

White matter: Bundles of axons, connecting neurons.

Basal ganglia: Four collections of gray matter located deep in the cerebral hemispheres.

Thalamus: The part of the brain which receives inputs from all the senses except for the sense of smell; this sensory information is associated, synthesized, and then relayed to specific areas of the brain. Impulses are also received from various parts of the brain and then relayed to nerve pathways leading to skeletal muscles.

Cortex: The outer layer of gray matter covering the cerebral hemispheres.

Prefrontal Cortex: The portion of the cortex found right behind the forehead. The most developed part of the brain in humans compared to other animals.

In 1986, Alexander and his colleagues pointed out that a number of discrete brain circuits could be identified. These circuits consist of prefrontal neurons that synapse in basal ganglia relay stations, which in turn send their signals to synapses in the thalamus, which in turn feeds back to the cortex (Alexander, et al., 1986). This "cortical-striatal-thalamic-cortical circuit" provides both positive and negative feedback to other regions of the brain and is believed to serve as the anatomical foundation of the executive functions.
While it is still far from completely understood, it is now possible to draw a simplified circuit diagram of the workings of the brain when controlling executive functions. I am not including that drawing here because it is too technical to be helpful to readers of ATTENTION!¨. Interested readers can find it in the July 1997 issue of Clinical Pediatrics from which this summary is taken. Suffice it to say that for now we are assuming that we have identified the brain circuitry and the neural pathways that control the brain's braking mechanism. Neuronal traffic through this pathway results in further increases in the level of inhibition normally produced by this system (Wichmann & DeLong, 1993).

This important pathway actually consists of two pathways: one we refer to as the indirect pathway and the other the direct pathway. Inadequate inhibitory activity in the indirect pathway or excessive activation via the direct pathway is believed to contribute to a number of disorders, including AD/HD, Tourette's Syndrome, and obsessive compulsive disorder. Since these three disorders can often be found in the same individual, this coincidence is not altogether surprising.

The Role of Dopamine in the Brain's Braking System

Dopamine is a neurotransmitter, or brain messenger, that travels across the synapses in the brain. The most convincing evidence of the importance of dopamine in normal functioning of the brain's braking system comes from Parkinson's Disease, in which symptoms of tremor, akinesia (complete or partial loss of muscle movement), and rigidity emerge after the death of dopaminergic neurons in certain parts of the brain. Simply put, the deficit in dopamine results in excessive inhibition.

While it may be simplistic to suggest that motor hyperactivity in children with AD/HD represents a type of reverse Parkinson's, several lines of evidence make this possibility worth considering. First of all, dopamine is developmentally active. Its concentration in cerebrospinal fluid (the fluid cushion protecting the brain and spinal cord) peaks at about the age of two and declines fairly rapidly over the next dozen years. It is another interesting coincidence that young children appear to have an "excess" of the particular neurotransmitter that facilitates exploration of their environment and that the

concentrations of this substance would generally decrease as children become older and less adventurous.

Dopamine and AD/HD

Dopamine is rapidly broken down into "metabolites" in the body after it is released. My colleagues and I at the National Institute of Mental Health were initially surprised to find that high levels of concentrations of dopamine metabolites in the cerebrospinal fluid correlated with high degrees of hyperactivity in twenty-nine boys (Castellanos, et al., 1994). We also found that the concentration of the dopamine metabolite in the cerebrospinal fluid was the best predictor of how improved the boys would be when they were given methylphenidate, dextroamphetamine, or pemoline. With all three medications, the boys with the greatest dopamine metabolite concentrations exhibited the best responses to treatment with medication.

These results were consistent with an older study that documented decreases in these cerebrospinal fluid dopamine metabolite after treatment with dextroamphetamine, with the degree of change in the neurotransmitter highly correlated with the degree of behavioral improvement (Shetty & Chase, 1976). Our results suggest that motor hyperactivity may be associated with larger concentrations of this metabolite in the part of the brain known as the caudate - such as would be found in a neurologically younger child (e.g., a preschooler)

Neuroimaging in AD/HD

The other source of evidence that supports a role for the basal ganglia inhibitory circuits (the braking mechanism) in AD/HD comes from brain-imaging studies. While we are still learning about potential problems, results of these studies increasingly point to both structural and functional brain differences in individuals with AD/HD.

The most well known of these studies are those that used positron-emission tomography (PET) to demonstrate decreased frontal cerebral metabolism in adults with AD/HD. Other investigators of brain function have measured local cerebral blood flow, which is known to closely approximate neuronal activity, with a variety of techniques including Xenon inhalation and single photon emission tomography (SPECT). Decreased blood flow has been found in a part of the brain known as the striatum (Lou, et al., 1990) and in prefrontal regions (Amen, et al., 1993). However, these results remain tentative because ethical limitations make it difficult or impossible to run these tests on children who are healthy for comparison (normal controls). A more promising technique may be blood oxygenation level-dependent functional magnetic resonance imaging, which makes it unnecessary to use ionizing radiation. A preliminary report using this new technology has once again shown decreased blood flow in the right caudate (one of the components of the basal ganglia), which reversed on optimal methylphenidate treatment.

Our own group has concentrated on using anatomic MRI to discern structural brain differences in fifty-seven boys with AD/HD compared to fifty-five boys who do not have the disorder. We found that the boys who do not have AD/HD had a significant asymmetry of the caudate, the right side being 3 percent larger than the left side, on average. In contrast, the boys with AD/HD demonstrated no asymmetry - the right and left sides were the same size. Most interesting, the degree of loss of asymmetry correlated with the boys' performance on tests of response inhibition; the greater the degree of normal asymmetry, the better their performance. We also found several other structural differences in the brains of the boys with AD/HD, all of which are consistent with a delay in maturational changes in these boys.

Taken as a whole, the brain-imaging studies lend substantial support to the prediction made in 1991 by Heilman and his colleagues that right-sided abnormalities of the prefrontal basal ganglia circuit (the brain's braking mechanism) would be found in AD/HD. Not all basal ganglia structures are implicated, however; again, this supports the linkage of AD/HD to prefrontal circuits that serve executive functions.

Conclusion

Neuroimaging studies, the role of dopamine in the brain's braking mechanism, and the fact that methylphenidate treatment has been shown to decrease dopamine concentrations all are contributing greatly to our understanding of what part of the brain is involved in AD/HD and how these brain systems actually work. As our knowledge of the basal ganglia structures increases, specifically the circuitry of the braking mechanism discussed in this article, we may be able to better tailor interventions and treatments to match the varied symptoms presented by AD/HD.

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