The growing prevalence and cost of ADHD calls for research to better understand the disorder.

Most of us can remember a classmate who could never sit still. If he wasn’t getting up and pacing the room, he was tapping his pencil on the desk or kicking his feet. And then there was the one who sat in the corner, daydreaming and looking out the window. She never disrupted the class, but when called on to participate, she might not know what was going on.

Today, both of these children might be evaluated for ADHD. First diagnosed 100 years ago, the disorder is characterized by excessively inattentive, hyperactive, or impulsive behaviors. Symptoms include having trouble focusing, interrupting conversations or activities, and missing important social cues.

In recent years, the diagnosis of ADHD has become common. Between 5 and 8 percent of school-aged children in the United States have been diagnosed, with boys outnumbering girls nearly three to one. About 60 percent of children diagnosed with ADHD will continue to show symptoms well into adulthood. ADHD is prevalent in many other industrialized nations as well. Recent studies suggest that the prevalence in Canada and Europe is comparable to that in the United States. This becomes particularly evident when those countries use similar diagnostic criteria.

Regardless of location, ADHD also comes with a steep economic price. Based on a 5 percent prevalence rate, recent estimates indicate ADHD costs between $32 billion and $56 billion each year in the United States alone.

Attention Deficit Hyperactivity Disorder

More than 5 percent of young Americans have been diagnosed with ADHD, according to a 2007 survey by the CDC.

Potential Causes

Researchers are learning more about what causes ADHD. Twin and family studies show that ADHD has a strong genetic influence. One study found that more than 25 percent of parents with ADHD had children with the disorder.

Genes involved in the transmission of the neurotransmitters dopamine and norepinephrine have been implicated. In addition, recent imaging studies have shown reductions in the transmission of these so-called catecholamine neurotransmitters in at least some people with the disorder. Because prefrontal brain circuits, which are normally involved in cognitive control, require an optimal level of catecholamine stimulation, reduced catecholamine transmission could potentially lead to the weakened regulation of attention and behavior in ADHD.

Altered brain activity also has been observed in circuits connecting the cortex, striatum, and cerebellum, particularly in the right hemisphere. Recent studies show a delay in cortical development in some children with ADHD, although most individuals with ADHD do not outgrow the disorder as they mature.

Children with ADHD often have cognitive deficits as well. Research has shown that many people with ADHD have difficulties with executive functioning, which includes the ability to maintain and manipulate information in the short term, as well as planning and motor control. Particular deficits have been reported in processing visual-spatial information. This can translate into specific academic issues, such as difficulties with math skills related to geometry, difficulty reading maps, and problems with spatial relations.

Behavioral and pharmacological approaches. On the behavioral side, children can be taught strategies for staying on task, such as following a detailed schedule, or for organizing materials. Sometimes a physician determines that behavioral support is not enough. Many children with ADHD may also need medication.

ADHD: Currently, between 4 and 6 million children in the United States take one of these medications, which reduce hyperactivity and impulsivity, help improve the ability to focus, and even improve physical coordination. In fact, medications are so effective in helping people with ADHD that a recent shortage wreaked havoc for many families.

Nonetheless, many parents express concern about giving their children a drug that is potentially addictive. Cocaine and methylphenidate, the active ingredient in Ritalin, act similarly to inhibit their brain targets, the catecholamine transporters. Further, many wonder whether ADHD is overdiagnosed, leading to the diagnosis and treatment of high-energy children who have difficulty in the classroom, but are medically normal.

Only better understanding of ADHD and the medications used to treat it will answer these concerns. Many researchers are pursuing this path, studying ADHD’s underlying mechanisms and working toward developing new tools for managing and deepening knowledge of this increasingly common disorder.
Brain chemical transporters, like the one for glutamate shown in yellow, may be important in human health and disease, including ADHD.

The study suggested that people with ADHD have lower levels of both dopamine receptors and transporters than other healthy adults. Recently, researchers in the laboratory of Randy Blakely, one of Amara’s early collaborators, identified a change in the gene sequence of the dopamine transporter associated with ADHD in people. Research showed this genetic change altered the distribution and function of dopamine transporters in cells. This research brings us one step closer to understanding the cellular and molecular underpinnings of ADHD.

Viewed together, this body of work is beginning to make the case that ADHD is the result of impaired function of the dopamine system. Beginning with Amara’s initial basic science investigation of transporter function, researchers are getting closer to identifying how ADHD affects the brain and why a stimulant is an effective treatment. This research may one day identify medications that can better target this system, easing problems associated with ADHD.

Understanding and Treating ADHD

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What has been particularly puzzling is why stimulants such as methylphenidate (Ritalin®) have a calming effect on people with ADHD — the so-called Ritalin paradox. Interestingly, studying addictive drugs such as cocaine has helped answer this question. That’s because cocaine and methylphenidate are quite similar. Research has shown that cocaine and other stimulants block cells from disposing of dopamine, a brain chemical that produces pleasurable feelings.

How does dopamine work? During pleasurable experiences, it is released into the synapse, the space between communicating brain cells. It then binds to receptors in the receiving cell that specifically recognize and respond to dopamine. In the sending cell, the dopamine transporter is responsible for the re-uptake and storage of the extra dopamine in the synapse. Cocaine blocks the transporters, causing dopamine to accumulate in the synapse.

This finding opened the door to a new research path. Research by SfN Past President Susan Amara made studying dopamine transporters in depth possible. Amara and her colleagues figured out how to clone the gene for another transporter, for the brain chemical norepinephrine. This breakthrough allowed Amara and others to identify and study the genes for many other neurotransmitter transporters, including the dopamine transporter. Now, researchers could study how drugs interact with transporters, how the transporters function under different conditions, and how they are regulated. They could also create mice without any transporters at all.

**Calming hyperactivity in mice**
The role for dopamine transporters in the Ritalin paradox became clear once researchers in Marc Caron’s laboratory began studying their function in “knockout” mice — mice bred to lack dopamine transporters. Studies showed these mice were unable to clear dopamine. Behaviorally, the mice were hyperactive, much like children with ADHD. At this point, the relationship between dopamine and ADHD began to emerge. It was further clarified when the researchers gave the knockout mice cocaine or amphetamines. As with many children with ADHD who take Ritalin, the drugs calmed the rats down, suggesting that without dopamine transporters, stimulants behave quite differently.

Further investigation, however, raised the concern that knockout mice were too far removed from children with ADHD, who did not lack dopamine transporters, to be a good research model. To address this issue, scientists made “knockdown” mice, mice that made fewer dopamine transporters. Although not as impaired as the knockouts, the knockdown mice were also hyperactive. And similarly, stimulant drugs calmed the knockdown mice. This study provided additional evidence of the connection between hyperactivity and the dopamine transporter.

**Research extends to humans**
Research in people has validated these mouse studies. Using positron emission tomography (PET) scans, researchers compared brain activity of adults with and without ADHD.

**Study on knockout mice**

**Knockdown**