

# Understanding Adolescent Brain Development and Its Implications for the Clinician

Aaron M. White, PhD\*

*Division of Medical Psychology, Department of Psychiatry, Duke University Medical Center,  
Box 3374, Durham, NC 27710, USA*

Adolescence is the stage of human development during which we make the transition from childhood dependence to adult autonomy. Soon after our bodies begin the physical metamorphosis of puberty, the brain undergoes a fascinating array of gene- and experience-driven modifications that prepare us to survive in the current cultural context. In essence, puberty reflects the physical changes that allow us to survive in the adult world, whereas adolescence embodies the psychological/neurologic changes that allow us to survive in the adult world as it is now. In this article, adolescent brain development will be explored, and the implications of such development for both normal and abnormal behavior during the teenage years will be discussed. As we will see, the neurologic changes that take place during adolescence provide incredible opportunities for personal growth but also enhanced vulnerabilities to consequences ranging from psychological disorders to substance abuse.

## **THE MALLEABLE DEVELOPING BRAIN**

The brain is a remarkably complex, still poorly understood organ. Hundreds of billions of neurons, 1 of the 2 key types of cells in the brain, bathe one another in chemical messengers that influence moment-to-moment changes in brain processing, behavior, and experience. Glial cells, the other main category of brain cells, nurture and sustain neurons by holding them in place, feeding them partially metabolized glucose, fighting immune battles, cleaning up debris, and forming a key part of the blood-brain barrier that regulates the flow of molecules in and out of the brain. The basic layout of the brain is encoded by genes, but the specifics of the wiring are dependent on experience. The malleability of the developing brain allows each individual to be customized to fit the demands of the environments in which he or she is raised.

---

\*Corresponding author.

*E-mail address:* aaron.white@duke.edu (A. M. White).

Until quite recently, it was generally believed that the majority of brain development is finished by the age of 10. Learning languages becomes much harder after this age, and the brain reaches its adult size at about this time. Indeed, the brain is 90% of its adult size by the age of 7.<sup>1</sup> The moodiness, risk-taking, rule-breaking, and general tumult of the adolescent years were long assumed to stem from the hormone changes of puberty. We now know that, although hormones certainly do contribute to the roller-coaster ride of adolescence, hormone changes are just part of the puzzle. Thanks in large part to research by Jay Giedd and colleagues at the National Institute of Mental Health, it has become clear that, during the adolescent years, the organization and functioning of the brain go through complex changes. Importantly, these changes seem to be unique to the adolescent years and not simply the trailing remnants of childhood brain development.

### **CHANGES IN THE FRONTAL LOBES DURING ADOLESCENCE**

Some of the most intriguing changes in the brain during adolescence take place in the frontal lobes. These brain areas, located just behind the forehead, play critical roles in memory, intentional movement, controlling emotional urges, making decisions, planning for the future, and other higher-order cognitive functions on which adults rely for survival. Frontal lobe gray-matter volumes, which represent dense concentrations of neurons and their parts, increase throughout childhood and do not reach their peak until approximately the age of 11 (girls) or 12 (boys), at which point they decline throughout the second decade of life and into young adulthood.<sup>1</sup>

Why might frontal lobe gray-matter volumes go up during childhood and down during adolescence? Recent data suggested that, during childhood, neurons in the frontal lobes are allowed to overgrow and form far too many points of communication, or synapses, with other neurons. As a result, gray-matter volumes increase. As childhood draws to a close and adolescence begins, the brain switches from overproduction mode to selection mode. Early in the second decade of life, the brain stops overproducing synapses in the frontal lobes and puts the synapses that exist on the chopping block. Hundreds of billions of points of communication will be sacrificed through the teenage years. Only those that form meaningful, useful points of contact will be kept. Guided by a teenager's experiences, the frontal lobes are shaped and molded into a configuration that will carry the individual, for better or worse, through the adult years. As this pruning process unfolds, gray-matter volumes decrease.<sup>2</sup>

The activity of neurons requires energy. As frontal lobe gray-matter volumes rise during childhood and fall during adolescence, a parallel increase in overall metabolism occurs in the frontal lobes during the first decade of life and then decreases during early adolescence, reaching adult levels by the age of 16 to 18.<sup>3</sup> Importantly, declines in gray-matter volumes and energy usage during adoles-

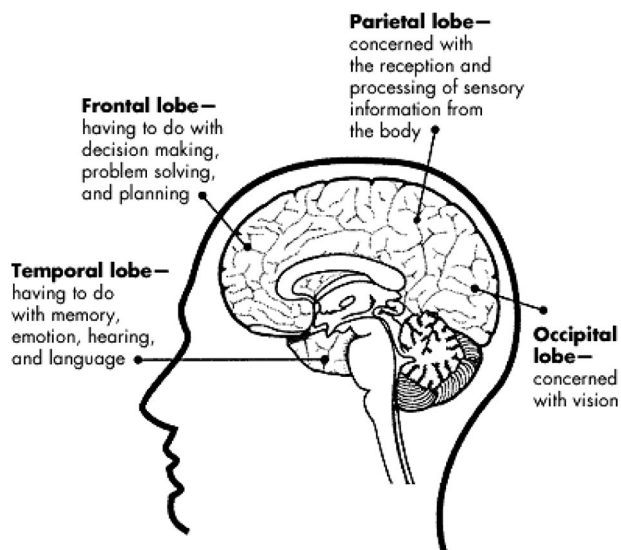


Fig 1. The human brain. (Reproduced with permission from National Institute on Drug Abuse. *Mind Over Matter: The Brain's Response to Drugs*. Teacher's Guide. Bethesda, MD: National Institute on Drug Abuse; 2002:10. Available at: <http://teens.drugabuse.gov/mom/teachguide/MOMTeacherGuide.pdf>).

cence do not reflect a diminution of frontal lobe function. Quite the opposite. As gray-matter volumes and metabolism decrease, neural activity during the performance of frontal lobe–dependent tasks becomes more focused and efficient, and the accuracy of performance improves.<sup>2</sup> The changes taking place in the frontal lobes during adolescence reflect a fine-tuning of circuitry that allows for enhanced efficiency and accuracy of functioning.<sup>4</sup> Indeed, there seems to be a general increase in reliance on the frontal lobes to organize and control behavior as we progress through the teenage years toward young adulthood. This developmental transition of power to the frontal lobes has become known as frontalization.<sup>5</sup> Concurrent molding of circuitry as frontalization unfolds means that each individual will learn to control impulses, make plans, and regulate emotions in ways consistent with the contingencies of the current culture. Such cultural-specific molding of behavior manifests in the generation gap that frustrates so many parents.

The frontal lobes do not function in isolation (see Fig 1). That is, they gather information and exert their influences by interacting with other brain areas. In addition to revealing that changes take place within the frontal lobes during adolescence, recent science has begun to shed light on how circuits formed between the frontal lobes and other structures develop during the second decade of life. The overall picture is one of increasing specialization of function within specific subregions of the frontal lobes and increasing cohesion between these subregions and the brain areas with which they interact. For instance, in the

Stroop interference task, in which subjects are shown words in different colors and must inhibit the tendency to read the words to name the colors, coordinated activity between the lateral prefrontal cortex and the basal ganglia, the lenticular nucleus of the striatum in particular, comes online during adolescence. Both the accuracy of performance on the task and the magnitude of activation of circuits involving the frontal lobes and basal ganglia increase throughout the adolescent years and into adulthood.<sup>6</sup> Similar age-related increases in activity within circuits involving the frontal lobes and basal ganglia have been observed in the tracking stop task, a response-inhibition task in which subjects must inhibit a response to a go signal if it is followed by a stop signal.<sup>7</sup>

## **CHANGES IN OTHER PARTS OF THE CORTEX**

The frontal lobes are not the only cortical areas that undergo construction during the adolescent years.<sup>8,9</sup> As with the frontal lobes, the amount of gray matter in the parietal lobes peaks at approximately age 11 and decreases throughout adolescence. Located on the sides and toward the back of the brain, the parietal lobes are primarily involved in processing sensations from the body and understanding spatial relationships such as where the body is relative to other objects in the world. They are also very important for interpreting and creating music, solving math problems, and other higher-order abstract cognitive functions.

In the occipital lobes, located at the back of the brain and entirely dedicated to processing visual information, gray-matter volumes increase throughout adolescence and into the early 20s.

The temporal lobes, which are critical for memory formation as well as processing auditory information and seeing detailed patterns and shapes, do not reach their maximum levels of gray matter until the age of 16 to 17, at which point they plateau. The temporal lobes contain the hippocampus, a structure that is central to creating an autobiographical record of what one does and what one learns.

Clearly, much of the cortex undergoes changes during adolescence, each area with its own unique progression.<sup>1,2</sup>

## **STRUCTURES INVOLVED IN EMOTIONAL REACTIVITY AND RISKY BEHAVIORS**

On the surface, changes in the frontal lobes and other cortical structures seem capable of explaining a wide range of typical adolescent behaviors, including difficulties inhibiting impulses and the tendency to measure the future in hours and minutes rather than weeks and days. However, Casey et al<sup>10</sup> were quick to point out that changes in the frontal lobes and other cortical areas cannot explain the whole of adolescent behavior, particularly when it comes to risk-taking and strong emotional reactions. The authors argued that, similar to adolescents, children have

immature frontal lobes, too, but do not exhibit the degree of risky behavior exhibited by many teenagers. According to the authors, “[a]dolescence is a developmental period characterized by suboptimal decisions and actions that are associated with an increased incidence of unintentional injuries, violence, substance abuse, unintended pregnancy, and sexually transmitted diseases.” Indeed, the National Center of Health Statistics has estimated that there are 13 000 adolescent deaths per year, 70% of which are caused by motor vehicle crashes, unintentional injuries, homicide, and suicide<sup>11</sup> and all of which are activities suggestive of problems with impulse control and the presence of strong and often maladaptive impulses.

Casey et al concurred that immature frontal lobes certainly help explain problems regulating impulses. Maturation of the frontal lobes leads to the ability to suppress inappropriate thoughts and actions and to forego short-term satisfaction in exchange for reaching long-term goals. Immature cognitive control centers make it easier for emotional impulses to break through to the surface and influence behavior, but what about the strong emotional impulses themselves? From where do they originate, and why are they so strong during adolescence? The authors suggested that several important emotional areas of the brain reach full operating power by midadolescence at a time when the frontal lobes are still in flux. Adolescents are driven by strong emotions arising from these areas and do not yet have the cognitive control necessary to stifle, consistently, these strong emotional urges. The fact that the frontal lobes are not yet working at their full potential simply makes it easier for these deep emotions to influence moment-to-moment changes in behavior.

In support of their position, neuroimaging studies suggested that, when making risky choices and processing emotional information, adolescents exhibit larger increases in activity in the amygdala and nucleus accumbens relative to the activity seen in children and adults.<sup>2</sup> The amygdala, a small almond-shaped structure located just in front of the hippocampus in the temporal lobes on each side of the brain, plays a prominent role in learning and evoking emotional responses, particularly negative emotional responses, to stimuli.

The nucleus accumbens, deep within the center of the brain, is the heart of the reward system. The nucleus accumbens receives signals in the form of the neurotransmitter, dopamine, from another deep-seated structure called the ventral tegmental area. This system is strongly activated both in anticipation of reward and on the delivery of reward. In essence, activation of this circuitry leads to pleasure, and pleasure increases the odds that the rewarded behavior will be repeated. Animal studies<sup>2</sup> have suggested that the density of dopamine receptors is highest in the nucleus accumbens during adolescence, perhaps making this region particularly responsive to the rewarding signals that dopamine provides. As will be discussed in a subsequent section, these poorly understood changes in the reward system are thought to contribute to the heightened risk of abuse and dependence people face when substance use begins during the adolescent years.

In addition to exhibiting differences in responsiveness to both fear-inducing and rewarding stimuli, adolescents exhibit an exaggerated stress response relative to children and adults.<sup>12</sup> This exaggerated stress response seems to contribute to the periodic difficulties that many teenagers have regulating their emotional reactions. At the core of the stress response is the hypothalamic-pituitary-adrenal (HPA) axis. In response to stressful stimuli or environments, the hypothalamus releases corticotropin-releasing hormone, which causes the pituitary to release adrenocorticotropin, which in turn triggers the adrenals, located just above the kidneys, to release cortisol. Puberty brings increased activity in the HPA axis. Sharp increases in urine and salivary cortisol levels happen at approximately the age of 13 and remain elevated into adulthood. A little cortisol goes a long way and helps the body prepare itself to deal with stressors and form memories of stressful events. Too much cortisol is associated with the onset of depression, the death of brain cells in the hippocampus, the memory center of the brain, and with weakened immune activity and cardiovascular problems down the road. Cortisol triggers anxiety via receptors on neurons in the amygdala, and high cortisol levels are commonly seen in adolescents, as well as children and adults, with anxiety disorders.<sup>13</sup> A stronger association exists between adverse life events and depression during adolescence than during adulthood, perhaps reflecting heightened reactivity in the HPA axis during the adolescent period.<sup>14</sup>

Additional evidence that adolescents are particularly reactive to stress comes from evidence that stressful stimuli cause greater skin-conductance changes in adolescents than in adults. In adolescents, these changes in skin conductance also take longer to habituate. In other words, the stress response is not only larger in adolescents than adults but also stays activated longer once initiated.

Collectively, heightened activity in the amygdala, reward system, and HPA axis, combined with the still-developing frontal lobe circuits, could explain the presence of particularly strong emotional impulses and reactions during adolescence and the trouble many adolescents have regulating them.

## **WHITE-MATTER VOLUMES AND PSYCHOLOGICAL DEVELOPMENT DURING ADOLESCENCE**

Most research on adolescent brain development has focused on changes in gray-matter volumes during the teenage years. As discussed above, gray-matter volumes reflect the density of neurons and parts of neurons. Understanding the changes that occur in neurons and the circuits they form during adolescence is critical if we are to understand adolescence as a neurodevelopmental stage. However, we also must understand the changes taking place in the other major category of brain matter, white matter.

White matter reflects the density of glial cells, which help protect and nurture neurons and the circuits they form. This diverse group of cells contains micro-

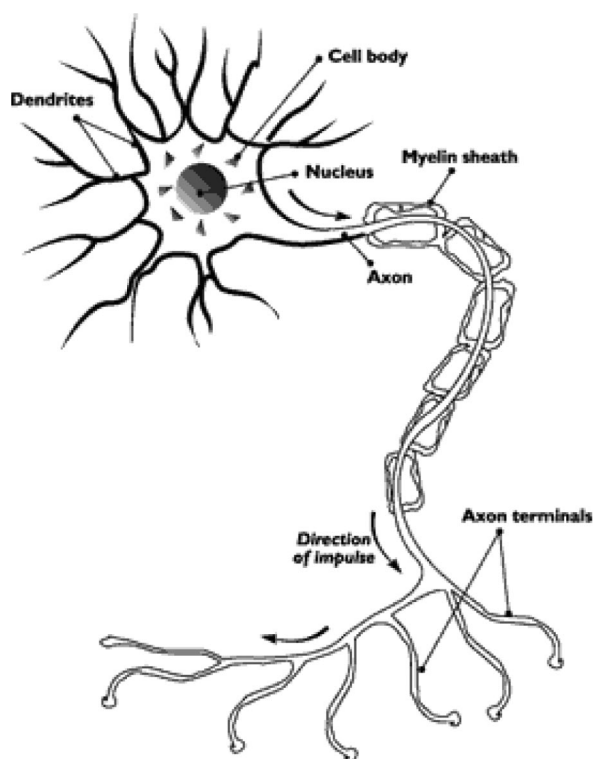


Fig 2. Depiction of a neuron. (Reproduced with permission from National Institute on Drug Abuse. *Mind Over Matter: The Brain's Response to Drugs*. Teacher's Guide. Bethesda, MD: National Institute on Drug Abuse; 2002:11. Available at: <http://teens.drugabuse.gov/mom/teachguide/MOMTeacherGuide.pdf>).

glia, which help fight brain infections, and astroglia, which form a critical component of the blood-brain barrier by surrounding blood vessels. Oligodendroglia, another type of glial cell, perform one of the most important acts performed by glia in the brain, namely, myelination of neuronal axons. Myelination will be discussed briefly, and then its role in adolescent brain development will be explored.

Neurons are capable of harnessing the electrical charges of ions (such as sodium, potassium, and chloride) located around their cell membranes to generate tiny electrochemical impulses called action potentials (see Fig 2). Action potentials begin near the cell bodies of neurons and travel down long arms called axons, which reach away from the cell bodies, branch out, and form synapses with other neurons. In essence, the axon is like a gun barrel down which the electrical impulse travels. Once the electrical signal reaches the distal tips of the axon, which could be several inches away from the cell body and number in the thousands by the time the axon stops branching, neurotransmitters are released onto the neuron's targets.

Myelination is a process by which oligodendroglia grab onto the axons of neurons and wrap around them. This increases the resistance across neuronal membranes relative to the resistance of the cytoplasm contained in the axons and allows action potentials to travel down the axon farther and faster. As such, myelination speeds processing times in the brain and reduces the amount of energy that neurons need to exert to send signals to one another. Myelination essentially supercharges circuits in the brain and allows them to function quicker and more efficiently.

As has been discussed, gray-matter volumes in the frontal lobes increase during childhood, peak early in adolescence, and then decrease as a result of experience-driven molding throughout the adolescent years. Although gray-matter volumes in the frontal lobes follow an inverted U-shaped function, white-matter volumes seem to increase linearly throughout development into young adulthood. In a general sense, myelination progresses in a posterior-to-anterior fashion, with myelination being completed in cortical areas toward the back of the brain before the completion of myelination in the frontal lobes. Increased myelination leads to increased efficacy of the brain circuits formed within the frontal lobes and between the frontal lobes and the structures with which they communicate.

Several studies have suggested that changes in white-matter volumes are associated with cognitive and emotional development during the adolescent years. An MRI-based technique called diffusion tensor imaging allows researchers to use the patterns of movement of water molecules to infer not just the volumes of white matter in various areas of the brain but also the coherence or maturation of myelinated circuits. Several studies have suggested that cognitive abilities improve as myelinated circuits mature. For instance, Nagy et al<sup>15</sup> observed an association between working-memory performance and maturation of fiber tracts connecting the frontal and parietal lobes. The thickness of the corpus callosum, a bundle of myelinated axons traveling between the left and right hemispheres of the brain, increases during adolescence, eventually reaching a larger size in females than in males. Increased thickness here reflects increased myelination of axons in the corpus callosum, which presumably allows the 2 sides of the brain to communicate faster and more efficiently.

The importance of the corpus callosum in organizing behavior is revealed in cases in which the tract is intentionally severed to prevent seizure activity in one side of the brain from spreading to the other side. When the corpus callosum is cut, signals cannot get from one side of the brain to the other. Although most people automatically integrate the activity arising on both sides of the brain into their experiences and behaviors from moment to moment, a person with a severed corpus callosum cannot. In fact, the 2 sides of the brain can actually end up competing with each other for control of the person's actions.

Several recent studies suggested that increases in white-matter volumes in the corpus callosum during adolescence are associated with improvements in cognitive abilities. Using diffusion tensor imaging, Fryer et al<sup>16</sup> observed that, during adolescence, the maturation of white matter in the corpus callosum is associated with improvements in vocabulary and reading abilities, visuospatial skills (such as copying complex line drawings), and psychomotor performance (such as reacting quickly and in a coordinated manner in response to stimuli). This was particularly true with regard to maturation of the splenium, which is located in the posterior portion of the corpus callosum and seems to reach full maturity later in adolescence than other regions of the corpus callosum. This is an exciting new area of research, and future studies should yield useful insight into the role of myelination in the corpus callosum and elsewhere in improved cognitive skills during the adolescent years.

### **ADOLESCENT BRAIN DEVELOPMENT AND TYPICAL TEENAGE BEHAVIORS**

Time-lapse recordings during the adolescent years would capture a true metamorphosis. The second decade of life brings a multitude of changes on psychological, physiologic, and neurologic levels. If life were a white-water rafting trip, adolescence would be the rapids. We enter adolescence as kids who tag along with adults and have our needs met for us. We exit as semiautonomous young adults responsible for meeting most of our own needs and perhaps the needs of our own children. Without the normal upheaval in behavior that adolescence brings, the transition to adult autonomy could not occur.

The changes taking place in the adolescent brain explain many of the behavioral quirks that make adolescence successful as a stage of development. Highly reactive emotional centers imbue adolescents with impulses to explore and take risks while simultaneously providing both a mild paranoia of adults in general and a desire to spend copious amounts of time with their peers. As such, these changes serve as biological wedges that insert themselves between developing adolescents and the adults around them, primarily their immediate caregivers. Development of sex-specific brain structures leads to increased motivation to attract members of the opposite, and sometimes the same, sex and to work hard to gain their attention and acceptance.<sup>17</sup> Although not reviewed in this brief article, these changes serve as a perfect example of the conceptual intersection between puberty (sexual development) and adolescence (psychosocial development). Remodeling of the frontal lobes during the adolescent years leads to a period of short-sightedness and difficulties with impulse control, which allows the strong emotions typical of the adolescent years to usurp control over behavior and get teenagers out of the house and into the world to socialize and learn the rules of the current culture.

All of the aforementioned changes serve valuable purposes and allow adolescence to work as a stage of change. However, the modern world provides a litany

of ultimately unhealthy options for rebellious and short-sighted teenagers. In addition, the changes in brain function during adolescence, particularly the shifting of control away from emotional areas to forward cognitive control centers, do not always go as planned. Collectively, the changes of adolescence provide both opportunity and risk, and development sometimes goes awry. Let us explore some of the pitfalls that developing adolescents face.

## **ADOLESCENT BRAIN DEVELOPMENT AND PSYCHOLOGICAL DISORDERS**

During adolescence, the frontal lobes are handed executive control over behavior, and interactions with the outside world allow the adolescent to learn how to use the frontal lobes to regulate emotional expressions and make forward-thinking decisions that trade short-term reinforcement for long-term gains. Unfortunately, this transition of power does not always go according to plan. Problems with this process seem to contribute to the development of a host of psychological disorders, from depression to schizophrenia.<sup>18</sup>

The age range of 15 to 19 is considered a “hazard period” with regard to the development of conditions such as bipolar depression.<sup>12</sup> Adolescent-onset bipolar disorder is associated with a poorer prognosis and more comorbidity. As is the case with most psychiatric conditions, a combination of biology (the first hit) and experience (the second hit) seems to trigger bipolar disorder in developing young people. It is likely that basic wiring maps for the brain handed down through genetics predispose some individuals to such disorders. Maladaptive learning during the maturation of cortical circuits can serve as the catalyst that ultimately leads to the condition.

As an example of the role that learning plays in the development of disorders during adolescence, research has indicated that cognitive styles are associated with the onset of psychopathologies such as depression. Things such as ruminating about problems, making generalized statements about one’s self-worth, etc, are common tendencies in those who develop these conditions. Depressive thinking involves the activity of brain circuits. As the brain learns to deal with life and solve problems, the tendencies it acquires affect how the individual interacts with the world, which in turn affects brain function and reinforces those tendencies. Circuits exercised during adolescence have the potential to become part of the default circuits used by the brain for daily functioning during adult life. As such, the acquisition of maladaptive cognitive styles is associated with, and ultimately contributes to, psychopathologies such as depression.

It remains unclear whether problems with brain circuitry come first and give rise to maladaptive cognitive styles and behaviors or if maladaptive cognitive styles and behaviors emerge first as a result of learning and then further contribute to unhealthy molding of the brain. What is clear is that brain pathology is part of

these conditions one way or the other. For instance, bipolar depression during adolescence is associated with reduced frontal lobe volumes. Once bipolar adolescents reach adulthood, they perform more poorly than controls on tests of attention and vigilance and show less activation in the prefrontal cortex during the performance of such tasks. They also have trouble with working memory and with shifting attention. Similarly, bipolar adolescents show reduced activation in the prefrontal lobes during performance of the Stroop test, which requires subjects to shift attention away from reading target words and respond on the basis of the color of the words instead.<sup>12</sup>

## **MEDICATION ISSUES AND THE ADOLESCENT BRAIN**

Research suggesting that various medications affect adolescents differently than adults comes as no surprise to most pediatricians. Drugs used for conditions such as depression work by causing often-subtle changes in neurotransmitter levels, including levels of serotonin (5-hydroxytryptamine), dopamine, and norepinephrine. The adolescent brain is a brain in flux and exhibits widespread changes in the levels of all 3 transmitters and their effects on neurons. Behaviorally, adolescents often have rapidly shifting baselines, which can make it difficult to assess whether medications such as those for depression are actually doing their job. For these reasons, antidepressants tend not to work well for teenagers, although they certainly do for some young patients. In their meta-analysis of clinical trials, the US Food and Drug Administration concluded that only 3 of the 15 trials they examined suggested that antidepressants are better than placebo treatment in adolescents.<sup>19</sup>

In cases where they are effective, there is no evidence that use of antidepressants causes long-term complications with brain and psychological development. However, because of brain-related plasticity, one could speculate that teenagers might be more prone to exhibiting the discontinuation syndromes now associated with many antidepressants.

Much has been written in the past few years about the risk of suicide in adolescents who take antidepressants. This issue is worth discussing here, because the implication is that antidepressants affect the adolescent brain in such a way that suicidal thoughts and behaviors could emerge. Do antidepressants increase the risk that a teenager will commit suicide? It does not seem so, but for a variety of reasons, kids on antidepressants are more likely to think about it.

In 2004, a 27-member panel of public representatives, psychiatrists, pediatricians, statisticians, and experts in several other fields concluded that there was no evidence of an increased risk of actual suicides among teenagers treated with antidepressants.<sup>20</sup> However, they did observe compelling evidence of an overall increase in suicidality, a category that includes both suicidal thoughts and suicidal behaviors, among treated teenagers (4% of treated teenagers relative to

2% of untreated teenagers). This finding led the Food and Drug Administration to issue a warning about the potential link between antidepressants and the risk of suicide in teenagers. In the years since, some researchers have challenged the block-box warning and asserted that antidepressants are safer and more effective for adolescents than earlier studies suggested.<sup>21</sup>

Why antidepressants might cause an increase in suicidality in adolescents is unclear. However, it is important to remember that, until adolescent brain development is complete, areas involved in emotional reactivity often hold sway over behavior. It has long been speculated that, early in the course of treatment with antidepressants, there is an activation of cognitive functions before emotional well-being is improved. As such, it would become easier for one to think about the strong emotional impulses attempting to influence behavior. If, at a deep emotional level, one feels that life is not worth living, the augmented cognitive capabilities could be spent thinking about those troubling feelings, particularly early in treatment. The hope is that emotional well-being eventually improves and frees the frontal lobes to think positive thoughts. Until that time, increased suicidality seems to be a real possibility for a small percentage of adolescents treated with antidepressants.

## **ADOLESCENT BRAIN DEVELOPMENT AND DRUG USE**

The adolescent brain is a true learning machine. A vast array of changes occur in the brain during these years. These changes seem to be driven by genes and hormones and modified along the way by experience. As during both childhood and adulthood, the reward system plays a central role in learning during adolescence. When the reward system is activated, the behaviors that lead to its activation are reinforced and are more likely to occur again in the future. Indeed, that seems to be the main purpose of the reward system: to reinforce behaviors that the brain assumes are good for the individual's survival and/or the survival of the species. Eating food, drinking fluids, and engaging in sexual activity are examples. The intensive learning-related changes that occur in the brain during adolescence combined with strong motivation to activate the reward system during this time can easily lead to the development of bad habits that can become stubbornly imbedded in brain circuitry.

Substance use is more likely to begin during adolescence than at any other time, and the odds that such behaviors will lead to problems down the road are higher when they begin during adolescence relative to adulthood. Drugs from nicotine to heroin all act, in part, by activating the reward system and essentially tricking the brain, and the brain's owner, into thinking something important and adaptive just happened. As such, each time an adolescent, or an adult, activates the reward system with drugs, the odds go up that the individual will repeat this behavior in the future. Each time the urge to repeat the rewarded behavior is expressed behaviorally and not prevented by the frontal lobes, the odds go down that the individual will be

able to muster the necessary frontal lobe strength to stop the behavior the next time the urge emerges. It is this learning related process that likely culminates in the loss of control that is characteristic of serious drug problems.

Adults with fully functioning frontal lobes are typically capable of keeping themselves from going back to drugs that activate the reward pathway in exchange for pursuing long-term goals. Strong emotional impulses that lead to reinforced behavior combined with still-fragile cognitive control centers makes it easier for adolescents to head down pathways involving substance abuse and other risky activities and to keep coming back for more. Because the brain learns so quickly during adolescence, the odds seem higher that substance abuse will become a lifelong problem if it begins, and is repeated, during the adolescent years. The behaviors can become firmly rooted in brain circuitry and are difficult to override once the window of enhanced malleability closes.

In addition to being at greater risk for developing drug habits through learning, it also seems that several drugs affect the brain differently during the adolescent years than during adulthood, and many of these differences do not bode well for teenagers. For instance, in rats, the reinforcing effects of nicotine are much stronger during early adolescence than during late adolescence or adulthood,<sup>22</sup> a finding that could help explain why most adult smokers actually become dependent on nicotine during adolescence.

Of the drugs known to affect adolescents and adults differently, alcohol is the most well studied. Research with humans has suggested that alcohol abuse during the adolescent years is capable of knocking normal development off track and can lead to lingering cognitive impairments. Brown et al<sup>23</sup> compared 15- to 16-year-old adolescents in an inpatient substance abuse treatment program to controls from the community on a battery of neuropsychological tests. Frequent drinkers ( $\geq 100$  total drinking sessions), particularly those who had experienced alcohol withdrawal, performed more poorly than controls on several tests, including tests of learning and memory.

In a longitudinal study of subjects, aged 13 to 19, recruited from treatment programs, Tapert and Brown<sup>24</sup> observed that a return to drinking after the program led to further declines in cognitive abilities, particularly in tests of attention, over the next 4 years. Once again, withdrawal from alcohol was a powerful predictor of such impairments. Similarly, Tapert et al<sup>25</sup> assessed neuropsychological functioning and substance use involvement at 7 time points during an 8-year period in subjects beginning, on average, at the age of 16 and ending at 24. Many of the subjects were assessed initially while in treatment and then tracked after their stay in the facility ended. Others were recruited from the community and then followed during the 8-year period. Cumulative levels of substance use, including alcohol use, were correlated with impairments in verbal learning and memory during the final assessment. The findings suggested that

heavy use of alcohol and other drugs during the teenage years predicts lower scores on tests of memory and attention when one is in their early to mid-20s and highlights the disruptive effects that substance abuse can have on healthy neuropsychological development during adolescence.

Additional research by Tapert et al explored the brain mechanisms underlying such developmental impairments. In 1 study,<sup>26</sup> alcohol-dependent young women and healthy controls between the ages of 18 and 25 performed tests of working memory and vigilance (attention) while brain oxygen levels were measured by using functional MRI. The sample sizes were not quite big enough to detect significant impairments in working memory, although a clear trend toward such impairments was observed. However, alcohol-dependent subjects exhibited significantly less brain activity while performing the working-memory task. Weaker activity was observed in several parts of the frontal lobes and in the parietal lobes.

A subsequent study with alcohol-dependent young women showed that alcohol-related cues, such as words associated with drinking, elicited craving and led to greater increases in brain activity in a variety of regions relative to controls,<sup>27</sup> thus establishing a link between craving for alcohol and brain function in key areas and yielding further evidence that the brains of alcohol-dependent young women function differently than those of their peers. Given that the adolescent brain is built to learn and that brain plasticity diminishes once the adolescent years end, it seems likely that these strong reactions to alcohol-related cues could stick around for quite some time and increase the risk of relapse down the road.

Additional studies with rats supported the differential effects of alcohol on brain function during adolescence relative to the adult years. For instance, the hippocampus, which is central to the formation of memories for facts and events, is far more sensitive to alcohol in adolescent rats than in adult rats. Less alcohol is required to suppress memory circuits in the adolescent, relative to adult, hippocampus.<sup>28</sup> Exposing rats to high levels of alcohol across a period of several days causes cell death in the hippocampus, frontal lobes, and other brain regions and does so at lower levels in adolescents relative to adults, although the mechanisms underlying such damage remain unclear. In addition, alcohol suppresses the birth of new neurons in the hippocampus and does so with greater ease in adolescent brains.<sup>29</sup> In humans, the hippocampus is smaller in alcohol-abusing adolescents.<sup>30</sup> Whether this is a result of the suppression of cell birth, the death of existing cells, both, or an alternative cause is unclear.

The particularly negative effects of alcohol on hippocampal function in adolescent brains could help explain why memory blackouts, amnesia for events that take place while one is drinking, are so common during the adolescent years. Research by White and Swartzwelder<sup>31</sup> suggested that ~50% of college students have experienced at least 1 blackout. A survey of >5000 recent high school graduates during the

summer before they started college revealed that more than half consumed alcohol in the 2 weeks before the survey, and of those who drank, 12% of males and females experienced at least 1 memory blackout during that 2-week period.<sup>32</sup>

Other structures seem to suffer from the negative effects of alcohol on adolescent brain development, as well. For instance, alcohol abuse during adolescence is associated with reduced sizes of both the amygdala and the corpus callosum. It also seems that alcohol interferes with the maturation of white-matter tracts in the frontal lobes, perhaps by suppressing the activity of genes associated with the creation of the myelin sheath.<sup>30</sup> Research with rats has suggested that glial cell functioning affected by alcohol during adolescence only partially recovers with prolonged abstinence.<sup>33</sup>

The ease with which the adolescent brain learns seems to apply to learning about alcohol at a neurochemical level, not just at a social and behavioral level. It has long been known that the earlier an adolescent is exposed to alcohol, the greater his or her odds of becoming dependent on the drug down the road. It seems that the rapid learning made possible by heightened brain plasticity during the adolescent years can work against healthy development when it applies to drinking alcohol and, perhaps, using other substances.<sup>34</sup> For instance, the initial development of tolerance to alcohol, a process that involves learning at a neurochemical level, is faster during adolescence than adulthood, and such tolerance remains evident for a much longer period of time in adolescent subjects compared with adults.<sup>35</sup>

The good news is that the enhanced brain plasticity of adolescence seems to lend itself to recovery and not just to the development of the initial problem. Research indicates that adolescent substance abuse treatment works, particularly when adolescents are motivated to improve.<sup>36</sup>

## **KEEPING ADOLESCENT BRAIN DEVELOPMENT ON TRACK**

The changes that occur in the adolescent brain seem to unfold as part of the larger, gene-encoded, hormone-aided developmental plan. However, the outcomes of these changes are strongly influenced by interactions between the individual and the outside world. Strong emotional impulses help propel kids out of their basements and into the world. How the individual regulates these strong emotional impulses is influenced by learning. Some learn to exercise effective restraint over their urges, whereas others learn to do what they feel like doing when they feel like doing it.

At any stage of development, individuals are motivated to meet particular psychological needs. The needs of adolescents are similar in many ways to those of children and adults, with accentuated needs to push away from family members, explore the world, take risks, maintain privacy, and spend increasing

amounts of time with their peers. Similar to children and adults, adolescents need to feel safe and secure, feel loved and accepted by those around them, and have a sense of purpose and meaning in life. These needs exist against the backdrop of rampant hormonal changes and physical development, as well as the neurologic metamorphosis explored above. When adolescents have outlets for their deep emotional urges to explore, take chances, and socialize, the odds increase that they will make it through the teenage years unscathed. Adolescents, and their parents, should be encouraged to explore healthy outlets for these urges, lest they translate into unhealthy behaviors aimed at satisfying them, such as substance abuse, risky sexual practices, aggression, bullying, and so on. Quite simply, when teenagers are busy doing activities that make them feel validated and independent, they are less likely to engage in unhealthy, misguided behaviors. Extracurricular activities such as sports, music, drama, and volunteer work are all good ideas for keeping adolescents busy and helping to guide their development in healthy directions. When healthy behaviors are modeled by the adults in a home, adolescents are more likely to develop healthy habits without the need for special interventions. Parents should be encouraged to explore options for engaging their adolescents in extracurricular activities and to ensure that the behaviors they model are healthy.

It is paramount that adolescents learn to recognize and regulate their emotional impulses. By the end of the teenage years, the frontal lobes will be firmly in the driver's seat and should be capable of providing the right balance of gas and brakes. Until that time, any activities that help teenagers learn to take responsibility for, and hopefully pride in, their actions will be useful in keeping frontal lobe development on a healthy course. Similarly, activities that teach teenagers to delay gratification, such as saving money for a desired purchase, can serve as useful exercises for the frontal lobes and useful training for adult life in general. Educating parents about the changes taking place in their adolescents' bodies and brains can help diffuse the tension that normally exists in such households and, hopefully, increase their patience with the often-unfamiliar teenagers living in their homes.

## **CONCLUSIONS**

As we enter the second decade of life, begin to test drive adult behaviors, and inch our way toward autonomy, our bodies, including our brains, enter a very unique and tumultuous period of flux that culminates in physical maturation and the development of neurologic circuits capable of governing responsible adult behaviors. The changes that take place in the brain during adolescence shift behavioral control away from emotional regions (amygdala, nucleus accumbens, cingulate) to cognitive control centers (the frontal lobes). These changes culminate in improved abilities to regulate emotional impulses and make rational, forward-thinking decisions.

In the years that lead up to adolescence, an overabundance of synapses are created in the frontal lobes and between neurons in the frontal lobes and the brain's structures

with which they communicate. Early in the second decade of life, the brain simultaneously begins to shift control over behavior toward the frontal lobes and places synapses formed by frontal lobe neurons and neurons in other brain regions on the chopping block. This kind of malleability allows each successive wave of adolescents to adapt to a unique and increasingly complex world.

Once we leave adolescence and enter adulthood, the malleability of the brain decreases, and it becomes increasingly difficult to make changes. Although it is certainly possible to teach an old dog new tricks, it is much easier to learn new tricks when we are young. The good news, although sometimes bad news, is that the way the teenaged brain is molded depends in large part on the environments in which teenagers grow. By constructing healthy environments, the potential inherent in the changing adolescent brain can be harnessed, and the odds that a given adolescent will make it into young adulthood cognitively and emotionally prepared for the rigors of adult life can be maximized.

## REFERENCES

1. Giedd J. Structural magnetic resonance imaging of the adolescent brain. *Ann NY Acad Sci*. 2004;1021:77–85
2. Ernst M, Mueller SC. The adolescent brain: insights from functional neuroimaging research. *Dev Neurobiol*. 2008;68(6):729–743
3. Chugani H. Biological basis of emotions: brain systems and brain development. *Pediatrics*. 1998;102(5 suppl E):1225–1229
4. Schweinsburg AD, Nagel BJ, Tapert SF. fMRI reveals alteration of spatial working memory networks across adolescence. *J Int Neuropsychol Soc*. 2005;11(5):631–644
5. Rubia K, Overmeyer S, Taylor E, et al. Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci Biobehav Rev*. 2000;24(1):13–19
6. Marsh R, Zhu H, Schultz RT, et al. A developmental fMRI study of self-regulatory control. *Hum Brain Mapp*. 2006;27(11):848–863
7. Rubia K, Smith AB, Taylor E, Brammer M. Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior during error-related processes. *Hum Brain Mapp*. 2007;28(11):1163–1177
8. Shaw P, Greenstein D, Lerch J, et al. Intellectual ability and cortical development in children and adolescents. *Nature*. 2006;440(7084):676–679
9. Lenroot RK, Schmitt JE, Ordaz SJ, et al. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. *Hum Brain Mapp*. 2009;30(1):163–174
10. Casey BJ, Jones RM, Hare TA. The adolescent brain. *Ann NY Acad Sci*. 2008;1124:111–126
11. Eaton DK, Kann L, Kinchen S, et al. Youth risk behavior surveillance: United States, 2005. *J Sch Health*. 2006;76(7):353–372
12. Alloy LB, Abramson LY, Walshaw PD, Keyser J, Gerstein RK. A cognitive vulnerability-stress perspective on bipolar spectrum disorders in a normative adolescence brain, cognitive, and emotional development context. *Dev Psychopathol*. 2006;18(4):1055–1103
13. Coplan JD, Moreau D, Chaput F, et al. Salivary cortisol concentrations before and after carbon-dioxide inhalations in children. *Biol Psychiatry*. 2002;51(4):326–333
14. Walker EF, Sabuwalla Z, Huot R. Pubertal neuromaturation, stress sensitivity, and psychopathology. *Dev Psychopathol*. 2004;16(4):807–824
15. Nagy Z, Westerberg H, Klingberg T. Maturation of white matter is associated with the development of cognitive functions during childhood. *J Cogn Neurosci*. 2004;16(7):1227–1233

16. Fryer SL, Frank LR, Spadoni AD, et al. Microstructural integrity of the corpus callosum linked with neuropsychological performance in adolescents. *Brain Cogn*. 2008;67(2):225–233
17. Nelson EE, Leibenluft E, McClure EB, Pine DS. The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychol Med*. 2005;35(2):163–174
18. Spessot AL, Plessen KJ, Peterson BS. Neuroimaging of developmental psychopathologies: the importance of self-regulatory and neuroplastic processes in adolescence. *Ann NY Acad Sci*. 2004;1021:86–104
19. Newman TB. A black-box warning for antidepressants in children? *N Engl J Med*. 2004;351(16):1595–1598
20. Lock J, Walker LR, Rickert VI, Katzman DK; Society for Adolescent Medicine. Suicidality in adolescents being treated with antidepressant medications and the black box label. *J Adolesc Health*. 2005;36(1):92–93
21. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683–1696
22. Belluzzi JD, Lee AG, Oliff HS, Leslie FM. Age-dependent effects of nicotine on locomotor activity and conditioned place preference in rats. *Psychopharmacology*. 2004;174(3):389–396
23. Brown AS, Tapert SF, Granholm E, Delis DC. Neurocognitive functioning of adolescents: effects of protracted alcohol use. *Alcohol Clin Exp Res*. 2000;24(2):164–171
24. Tapert SF, Brown SA. Neuropsychological correlates of adolescent substance abuse: four-year outcomes. *J Int Neuropsychol Soc*. 1999;5(6):481–493
25. Tapert SF, Granholm E, Leedy NG, Brown SA. Substance use and withdrawal: neuropsychological functioning over 8 years in youth. *J Int Neuropsychol Soc*. 2002;8(7):873–883
26. Tapert SF, Brown GG, Kindermann SS, Cheung EH, Frank LR, Brown SA. fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcohol Clin Exp Res*. 2001;25(2):236–245
27. Tapert SF, Brown GG, Baratta MV, Brown SA. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. *Addict Behav*. 2004;29(1):33–50
28. White AM, Swartzwelder HS. Hippocampal function during adolescence: a unique target of ethanol effects. *Ann N York Acad Sci*. 2004;1021:206–220
29. Monti PM, Miranda R, Nixon K, et al. Adolescence: booze, brains, and behavior. *Alcohol Clin Exp Res*. 2005;29(2):207–220
30. Clark DB, Thatcher DL, Tapert SF. Alcohol, psychological dysregulation, and adolescent brain development. *Alcohol Clin Exp Res*. 2008;32(3):375–385
31. White AM. What happened? Alcohol, memory blackouts, and the brain. *Alcohol Res Health*. 2003;27(2):186–196
32. White AM, Swartzwelder HS. College bound students drink heavily during the summer before their freshman year. *Am J Health Educ*. 2009; In press
33. Evrard SG, Duhalde-Vega M, Tagliaferro P, Mirochnic S, Caltana LR, Brusco A. A low chronic ethanol exposure induces morphological changes in the adolescent rat brain that are not fully recovered even after a long abstinence: an immunohistochemical study. *Exp Neurol*. 2006;200(2):438–459
34. Carpenter-Hyland EP, Chandler LJ. Adaptive plasticity of NMDA receptors and dendritic spines: implications for enhanced vulnerability of the adolescent brain to alcohol addiction. *Pharmacol Biochem Behav*. 2007;86(2):200–208
35. White AM, Bae JG, Truesdale MC, Ahmad S, Wilson WA, Swartzwelder HS. Chronic-intermittent ethanol exposure during adolescence prevents normal developmental changes in sensitivity to ethanol-induced motor impairments. *Alcohol Clin Exp Res*. 2002;26(7):960–968
36. White AM, Jordan JD, Schroeder KM, Acheson S, Hanusa B, Swartzwelder HS. Predictors of relapse and treatment completion among marijuana-dependent adolescents in an intensive outpatient substance abuse program. *Subst Abus*. 2004;25(1):53–59