The Neurobiology of Adolescent Addiction

Michael Boucher

The neurobiology of adolescent addiction involves a complex interaction of different parts of the brain as well as different neurotransmitter systems. And while many details remain unclear at this point, we are learning more and more about the process of addiction and its relation to risk-taking behavior in adolescents. Our goal in writing this chapter is to elucidate the mechanisms and hypotheses that currently explain a majority of what is known regarding neurodevelopmental changes in adolescence and their impact on addiction. It is important to note that a great deal of the conclusions drawn from the experimental research at this point relies heavily on correlation and that causation has not been proven in the majority of cases. As our knowledge of the human brain and its development continues to grow, we are hopeful that we will have an even larger body of evidence supporting these conclusions.

This chapter focuses on the neurobiology of adolescent substance abuse and addiction. We explore the relationship between risk-taking behavior, substance use and abuse, and adolescent developmental neurobiology. The chapter is divided into four sections. First, we describe normal adolescent brain development. Next, we propose a psychological and biological model of adolescent addiction and risk-taking behavior. Then, we summarize the latest research on the neurobiology of adolescents at risk for substance abuse. Finally, we discuss the neurotoxic effects of substance abuse on the adolescent brain.

ADOLESCENT BRAIN DEVELOPMENT

Most brain growth occurs during the first 10 years of life, but the adolescent brain continues to mature via axonal growth, myelination, and synaptic pruning [1]. Myelination is the glial cell deposition of myelin around axons, insulating the neural connections, resulting in faster and more efficient neural circuitry. Synaptic pruning refers to the removal of excess, unhelpful connections (synapses) between neurons. The child’s brain has trillions of synapses between neurons. As the child’s brain responds to the environment and learns new skills and behaviors, certain connections are used, retained, and strengthened, and those connections that are not used are eliminated via synaptic pruning. This results in the development and use of dedicated connections and neural circuits, improving efficiency and reducing metabolic demand. It is important to recognize that this is a longitudinal process and that any distinct milestones tend to be variable from one individual to another.

Changes in Gray Matter and White Matter
Two major trends occur during this developmental process: the decline of gray matter and the growth of white matter. We divide the brain into gray matter and white matter based on early pathology studies that recognized that the brain has two distinct layers of color: gray and white. The gray layer, or gray matter, is composed mainly of neural cell bodies, where the cell’s nucleus and genetic material is stored. Gray matter volume peaks at age 13 and then begins to decline in volume and thickness, beginning first in the striatum and sensorimotor cortices, progressing to the frontal poles, and ending with the dorsolateral prefrontal cortex [1].

The cerebral cortex is the gray matter on the outer surface of the brain, and we measure the thickness of the cortex over the course of time and in certain diseases and conditions. During adolescence, the brain undergoes marked cortical thinning, most strongly in the parietal lobe, the medial and superior frontal regions, the cingulum, and the occipital lobe. It is believed that decreases in volume and thickness come from selective synaptic pruning, reduction in glial cells, and decreased intracortical myelination [1].

White matter is composed mainly of myelinated axonal tract and is defined by the relatively white appearance of its myelin sheath, and by the absence of neural cell bodies. In contrast to gray matter’s volume reduction, the white matter volume increases during adolescence, most strongly in the fronto-parietal regions [1]. To study white matter, researchers are now using a new neuroimaging technique called diffusion tensor imaging (DTI), which uses the diffusion properties of water molecules to explore white matter anatomy in finer detail. Two variables used to describe the white matter quality and architecture are fractional anisotropy (FA) and mean diffusivity (MD). High FA values mean greater myelination and fiber organization, whereas low MD values mean greater white matter density. DTI studies of normal adolescent brains show age-related increases in FA and decreases in MD. The most prominent FA changes during adolescence occur in the superior longitudinal fasciculus, superior corona radiata, thalamic radiations, and posterior limb of the internal capsule. Fiber tracts of the fronto-temporal pathways mature relatively later [2].

There is a temporal relationship between gray matter volume reduction and white matter growth and development. Temporally, the dorsal parietal and prefrontal brain regions experience concomitant gray matter volume reductions and white matter growth and DTI-demonstrate strengthening, though the biological underpinnings of this developmental cross-talk have not yet been well described [1].

Gender and the Brain

As male and female bodies differentiate significantly during adolescence, the male and female brains begin to show differences as well. Male children and adolescents have larger overall brain
volumes and proportionally larger amygdala and globus pallidus volumes. Female children and adolescents have larger caudate nuclei and cingulate gyrus volumes. Girls’ gray matter volumes typically peak 1–2 years earlier than boys’, whereas male adolescents have larger gray matter volume reductions and white matter volume increases. While both genders have the most prominent white matter growth in the frontal lobes, boys have larger white matter volumes around the lateral ventricles and caudate nuclei [1]. Finally, white matter growth in boys is marked by an increase in axonal diameter, with testosterone as a possible etiological factor, whereas white matter growth in girls is driven by an increase in myelin content, with luteinizing hormone associated with greater white matter content [3]. The functional significance of these differences is not known and caution is urged before ascribing explanatory power to these preliminary findings.

THE NEUROPSYCHOLOGY AND NEUROBIOLOGY OF ADOLESCENT RISK-TAKING BEHAVIOR

The preceding section briefly described the neuroanatomical development of the adolescent brain. These changes most likely underlie the primary cognitive and psychological maturations seen in the adolescent development of executive function, which includes tasks such as complex decision-making, self-monitoring, impulse control, and delay of gratification. A popular hypothesis regarding the neuroanatomical correlate of executive function lies in the functional and anatomical relationship between the prefrontal cortex (PFC) and the ventral striatum (VS). In many adolescents, poor executive function is associated with increased risk-taking behavior, and can be theoretically viewed neurobiologically as an unequal relationship between the prefrontal cortex and the ventral striatum.

It has been well demonstrated that adolescents engage in more risk-taking behaviors than their younger and older counterparts, including more experimental substance use [4]. Adolescents are described as impulsive and greater risk-takers, and while these two terms are often conflated, it is very important to distinguish impulsivity from risk-taking across cognitive and neuranatomical domains. One hypothesis that is gaining popularity states that impulsivity is thought to arise from poor “top-down” cognitive control from the prefrontal cortex, and that risk-taking is related to sensation-seeking behavior driven by the ventral striatum.

Impulsivity in adolescence can be seen as a form of poor cognitive control. Cognitive control is defined as the ability to resist temptation in favor of long-term goals, or the ability to delay immediate gratification. Operationalized, it is “the ability to accomplish goal-directed behavior in the face of salient, competing inputs and actions” [5]. Developmental studies demonstrate that cognitive control shows linear improvement from infancy to adulthood, correlating with the pattern of myelination of the prefrontal cortex [6]. Clinically, we observe this behavioral control in the go/no-
go task, the Simon task, and the task-switching paradigms, when we are asked to suppress the pre-programmed response to achieve the correct alternative response. For example, imagine the following:

A child, adolescent, and adult are all trained to clap their hands when the light turns blue. Thirty times the light turns blue, and thirty times they clap. Then, we change the rules, and ask them to tap their feet when the light turns blue. The impulse is to clap, and it is hardest for the child and easiest for the adult to control that impulse and adapt to the new rule. The first 10 times the light turns blue, the child claps by impulse six times, the adolescent four times, and the adult two.

Cognitive control increases linearly with age, but when rewards are linked to behavior, this linear development gets skewed. When we receive an appealing award for completing a task demanding cognitive control, our performance improves. However, when we must suppress an impulse that is linked to an appealing cue, our performance suffers [5]. This idea should fit well with our basic understanding of human nature. When we are rewarded for good behavior, we are more likely to perform that behavior. This is the basis of positive reinforcement. However, for the person on a diet, it is harder to resist an appealing appetizer than the bland sandwich, even though both have the same number of calories. This relates to our basic understanding of addiction: initially, the behavior – drug use – is linked to a positive reinforcement, the euphoria or “high” we experience from the drug, and we quickly learn to like using drugs. However, when we try to stop using the drug, we are trying to choose the behavior – abstinence – that has little to no immediate positive reward associated with it. Thus, in choosing abstinence, we are choosing against the behavior, drug use, that has the appealing reward. This choice is hard, and the more times we use the drug, the harder it becomes to choose abstinence, because our brain is strengthening the link between the behavior and the reward. To compound matters further, after continued drug use, our brain adjusts its response and begins to depend on the drug to feel “normal.” We begin to crave the drug, and now choosing abstinence not only has no positive reinforcement, but also negative reinforcement: the craving to feel “normal.” At this point, we have reached physiological addiction, and in order to get the euphoria from the drug, we must use an increasing quantity and potency each time. Finally, now that we are addicted and we get less euphoria for each unit of drug use, we experience less reward.

It is a rather simple concept that appealing behaviors are easy to choose and hard to ignore. However, this concept will be explored in detail because, as it turns out, adolescents are much more sensitive than children or adults to these motivational incentives. The teenager is highly responsive to positive reinforcement, but is also highly driven towards appealing-through-dangerous enticements.
In many behavioral studies, adolescents are more sensitive than adults to the promise of financial rewards for accurate performance. In other words, their performance improves more than adults because they are more motivated by the financial reward [7]. This also holds true for social rewards as simple as a happy face. However, this heightened response to rewards can lead to riskier decisions. In gambling studies, adolescents will make riskier decisions than adults or children, but only when they know they will be given immediate feedback on their gamble [8]. Knowledge of this immediate feedback elicits an emotional response, and this emotional activation promotes riskier gambles. In the delayed feedback group, the participant is given 30 playing cards, all face down in a grid. He is asked to choose how many playing cards to flip over, and for each red card he will receive $10, but for each black card he will lose $5. He picks his cards all at once and awaits the results. In the immediate gratification group, the participant selects cards one at a time, flipping each card over and finding out if she won or lost money, then being told how many red cards were left. In the delayed group, adolescents and adults did not significantly differ in their gambling risk, but in the immediate gratification group, adolescents were significantly riskier gamblers than adults [8].

Social incentives, ranging from a happy face to peer group acceptance, also influence cognitive control most strongly in adolescents. From epidemiological studies, we know that teenagers are much more likely to try drugs or alcohol if their peers are using substances [9]. On a simulated driving test, adolescents are riskier and more dangerous drivers when peers are in the car than when they are alone, and this risk decreases with age [10].

These findings suggest that risk-taking behavior is the result of the interplay between cognitive control and sensitivity to rewards. While cognitive control increases in a linear fashion with age, sensitivity to rewards appears to peak in adolescence, with teenagers more influenced by rewards than their younger and older counterparts. While toddlers and children are very impulsive, they are also fairly risk-averse, displaying lower sensation-seeking and reward sensitivity. At the other end, adults have reached their maximum level of cognitive control, and they are better able to suppress their motivational, sensation-seeking drives. Adolescents fall right in the middle, but unlike Goldilocks, their motivational drive is too hot and their cognitive control is too cold.

Functional Neuroanatomy and the Neuroimaging Correlates of Cognitive Control and Reward Sensitivity

Galvan et al. [11] propose a neurobiological model of adolescent risk-taking behavior that implicates the prefrontal cortex as the location of cognitive control, and the ventral striatum as coordinator of reward sensitivity. Goal-directed behavior is driven by the interaction between the prefrontal cortex and the ventral striatum, and risky behavior occurs when there is an imbalance in the circuit.
between the prefrontal cortex and the ventral striatum, henceforth known as the frontostriatal circuit. First, let us define our terms.

The prefrontal cortex (PFC) is located in the anterior part of the frontal lobes of the brain, and the PFC is the primary neuroanatomical location of cognitive control. The development of the PFC is linear, as evidenced by DTI studies of myelination, and the human brain does not complete myelination of the PFC until at least 25 years of age [12]. Clinically, we see impulse control develop linearly, and functional magnetic resonance imaging (fMRI) studies correlate PFC activation with impulse control.

The ventral striatum and the dorsal striatum make up the neostriatum, which is part of the basal ganglia, along with the substantia nigra, globus pallidus, and the subthalamic nucleus. The neostriatum is divided by its anatomical and neurochemical boundaries into the dorsal striatum, made up of the caudate and putamen, and the ventral striatum, consisting of the nucleus accumbens and the olfactory tubercle. The ventral striatum is strongly innervated by dopaminergic fibers from the ventral tegmental area (VTA), a key anatomical player in the mesolimbic dopamine system and highly implicated in all addictive and motivational behaviors [13]. The ventral striatum (henceforth VS) is implicated in motivational drives and sensation-seeking behavior, and appears to be most active during adolescence, as our review of the research will indicate.

Thus, Galvan’s model hypothesizes the following:

1. Substance abuse during adolescence can be thought of as a form of risk-taking behavior.
2. Risk-taking behavior is psychologically modeled by the interaction between cognitive control and motivational drives. Risky behavior occurs when the motivational drive is “stronger” than the cognitive control
3. Risk-taking behavior peaks during adolescence, with children’s behavior being “too timid” and adults’ too “in control”.
4. Neuroanatomically, cognitive control is found in the PFC, and the motivational drive is driven by the VS.
5. During adolescence, the VS is hyperactive compared to its child and adult states, overwhelming the still immature PFC, and ultimately correlating with the adolescent’s peak in risk-taking behavior.

Evidence for the first three points has been presented in the preceding sections. The last two points concern the neurobiology of risk-taking behavior, and evidence for those contentions is reviewed below:
1. Risk-taking behavior is a form of goal-directed behavior, and the frontostriatal circuit is necessary for learning goal-directed behavior.

   Using lesion studies and single-unit neuronal recordings, we have discovered that when monkeys and humans learn goal-directed behaviors, the VS is activated early on to learn and remember the association between behavior and reward. The PFC later is engaged in maintaining and optimizing behavioral patterns to receive the reward [14].

2. The neuroanatomy of the frontostriatal circuit changes during adolescence.

   As highlighted earlier, the frontal-temporal white matter circuitry undergoes significant growth in myelination and axon strength during adolescence. DTI and fMRI studies show that the frontostriatal circuit is strengthened via myelination and axonal size during adolescence, and that the strength of the circuit’s connection is temporally related to people’s ability to display cognitive control [1]. Dopamine receptor density in the striatum peaks early in adolescence, while in the PFC, dopamine receptor density peaks later in young adulthood [12]. It is unclear exactly how dopamine receptor density changes affect behavior, but it is thought to be functionally related to sensation-seeking behavior.

3. Ventral striatal activation is sensitive to reward, and most sensitive during adolescence.

   Galvan has linked the behavioral studies of reward sensitivity to VS activation, showing that the VS activation was sensitive to the amount of financial reward, and this response was strongest in adolescent brains, showing either signal increases or longer activation [15]. VS activity is positively linked to a self-reported likelihood to engage in risky behavior[11]. Previous imaging studies with adults have also linked the VS activity with risky choices [16].

   - Van Leijenhorst et al. [17] studied gambling, and showed increased VS activation during high-risk gambles, and increased PFC activation during low-risk gambles.

4. Prefrontal cortex activation is related to cognitive control and impulsivity. There is a significant body of evidence documenting PFC activation during impulse control tasks, and as people age the recruitment of PFC is stronger, and impulse control better. Ratings of impulsivity are inversely correlated with brain volume in the PFC [18], and disorders of impulsivity like attention-deficit/hyperactivity disorder demonstrate decreased activation in prefrontal regions compared with controls [19].

   - The PFC, and the science of brain localization in general, gained widespread attention following the curious case of Phineas Gage. On 13 September 1848, 25-year-old Phineas Gage was working as a railroad foreman in Vermont, preparing to blast away rock to clear land for the
developing railway. Gage added the blasting powder into a burrowed hole in the rock, and used a large iron rod to compress the charge. By tragic accident, the fuse lit early, the powder exploded, and the large iron rod flew from the hole, entered the left side of his face, through his left eye, and out the top of his head. Amazingly, Gage survived, but eventually those around him noticed a distinct change in personality [20], as described eloquently by his doctor, John Martyn Harlow [21]:

The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operations, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. Previous to his injury, although untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart businessman, very energetic and persistent in executing all his plans of operation. In this regard his mind was radically changed, so decidedly that his friends and acquaintances said he was "no longer Gage."

From this tragedy, neurologists began to speculate about the function of the part of Gage’s brain that was injured. Gage donated his brain to science, and modern researchers have confirmed what Harlow originally posited, namely that Gage suffered severe damage to his left frontal lobe, but all other brain areas were spared. Clinically, as Harlow described, Gage’s personality changed drastically: he became impulsive and seemingly governed by his desires. His story serves as a famous and useful reminder of the power of the frontal lobe, and the PFC in particular, in controlling our impulses and restraining our desires.

5. The frontostriatal circuit responds to reward-based cognitive control.

- We previously discussed that rewards improved cognitive control, most strongly in adolescence. Geier et al. [22] present evidence for the neural substrate of this enhanced cognitive control, using fMRI during the anti-saccade task. The anti-saccade task is a common experimental tool to study flexible control over behavior. As explained by Douglas et al. [see ref. 23], “In this task, participants must suppress the reflexive urge to look at a visual target that appears suddenly in the peripheral visual field and must instead look away from the target in the opposite direction. A crucial step involved in performing this task is the top-down inhibition of a reflexive, automatic saccade.” In the study, monetary reward resulted in improved performance, most strongly in adolescents.
Anatomically, adolescents showed exaggerated activity in the VS, as expected, and increased activity in the precentral sulcus within the PFC – involved in controlling eye movements – providing visual evidence for the reward-related upregulation in cognitive control.

- Additional evidence highlights the neural correlates of diminished cognitive control when faced with appealing alternatives. Somerville et al. [24] tested the go/no-go task with neutral and appealing cues (happy faces). When faced with neutral cues, children, adolescents, and adults all show gradual improvement with practice. The prefrontal cortex activation was associated with accuracy and showed linear changes with age of participant. However, when forced to choose against the appealing cue, adolescents didn’t show the steady improvement expected by their neutral performance, and this reduced cognitive control was paralleled by increases in VS activation.

In summary, we postulate that adolescent substance abuse can be seen as an example of risky behavior. Adolescents have consistently been demonstrated to engage in more risky behavior than either children or adults. Neuropsychological research suggests that this risky behavior is the result of highly active motivational drives exerting exaggerated influence over cognitive control. Neurobiologically, it can be inferred that in the adolescent brain, which has a hyperactive VS actively seeking out rewards, and an immature, poorly myelinated PFC, a struggle to control impulsivity will inevitably ensue.

The Role of Neurotransmitters in Risk-Taking Behavior: Serotonin and Dopamine Receptor Systems

Neurotransmitters are amino acids, peptides, and monoamines that transmit signals from a neuron to a target cell across a synapse. Several neurotransmitter systems exhibit change and development in the adolescent brain. This section focuses on the roles of dopamine and serotonin. The details are nuanced, confusing, and still being discovered, but the take-home message (based on current research) is straightforward: Dopamine is a driving force in all addictive and risk-taking behaviors, and it acts directly on the frontostriatal circuit. Serotonin (5-hydroxytryptamine, or 5-HT) acts as a brake on dopamine, and works to curb impulsive, sensation-seeking, and addictive behavior. First, we will describe the development of the dopamine and serotonin neurotransmitter systems. Then we will look at their role in risk-taking behavior and addiction.

Dopamine is a catecholamine neurotransmitter produced in the ventral tegmental area (VTA), the hypothalamus, and the substantia nigra, along with other brain areas. There are four major pathways through which dopamine exerts its effects: the mesocortical pathway, connecting the VTA with the PFC; the mesolimbic pathway, connecting the VTA to the nucleus accumbens, amygdala,
and hippocampus; the nigrostriatal pathway, connecting the substantia nigra with the basal ganglia and dorsal striatum; and the tuberoinfundibular pathway, connecting the hypothalamus with the pituitary gland. Given the wide distribution of dopamine, it is not surprising to learn that it has many effects on the brain. In this chapter we are most interested in the mesolimbic and mesocortical pathways, connecting the VTA with the PFC and the nucleus accumbens. Notably, another major psychiatric illness is also modeled as a disease of dopamine dysregulation. Schizophrenia is defined by positive symptoms (hallucinations, delusions, and bizarre behavior) and negative symptoms (blunted affect, poverty of speech, anhedonia, asociality, and avolition). The dopamine hypothesis for schizophrenia [25] posits that the positive symptoms are driven by excessive activation of D2 receptors in the mesolimbic pathway. Typical antipsychotic medications block D2 receptors and work primarily to lessen the positive symptoms of schizophrenia; many of these medications’ side effects are through inadvertent blockade of dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

When a person is exposed to novel situations, risky behaviors, or intoxicating substances, the VTA releases dopamine into the nucleus accumbens (NAc). The NAc is activated, evaluates the exposure’s appeal, and sends projections to the PFC, amygdala, and other brain areas to influence the person’s behavior and memory regarding the exposure. In a simplified interpretation, the more dopamine that is released into the NAc, the more it likes the exposure, and the more likely it is we will want that exposure again. Food, sex, and drugs all are associated with dopamine release in the NAc. Certain drugs, like cocaine, cause strong releases of dopamine into the NAc, inducing significant desire as well as neuroplastic changes to the downstream circuits that are thought to be hallmarks of the development of addiction [12].

The dopamine receptor profile changes dramatically in the brain’s anatomical reward circuitry – the PFC and the NAc. The density of D1 and D2 receptors peaks in the striatum early in adolescence, followed by loss of these receptors by young adulthood. In the PFC, the D1 and D2 receptor density does not peak until late adolescence. DA fiber density increases in the PFC of adolescent rats and NAc of gerbils, and DA inputs to the primate PFC peak in adolescence [26]. It must be noted that the significance of these findings is not yet clear.

Serotonin is produced in the raphe nucleus and projects to the PFC, NAc, hippocampus, and limbic system [27]. NAc serotonin turnover is four times lower in adolescent rats than in younger or older rats [28]. In men, serotonin receptor binding decreases the most during adolescence [29]. There is some evidence that serotonin input to the NAc is underdeveloped compared to dopamine input to the NAc during adolescence [12]. In functional studies, serotonin is found to be important to control and shape dopamine-related learning. In control rats, conditioned behavior (as driven by dopamine)
extinguishes after prolonged absence of the cue. However, when rats were exposed to a chemical (MDMA) that is toxic to serotonin projection, they continue to perform the conditioned behavior for more than a week in the absence of the behavioral cue [30]. In other words, without serotonin, there was no brake on the dopamine-driven learned behavior. Similarly, other studies have shown higher serotonin activity correlated with less aggression and impulsivity [31].

AT-RISK ADOLESCENTS: AT-RISK FOR DISINHIBITION

Risk-taking behavior is a hallmark of adolescence, and while it is common for teenagers to experiment with illicit substances, most adolescents do not develop drug addictions, or substance use disorders (SUD). Identifying the at-risk adolescent is a primary goal of public policy, and understanding the neurological markers for at-risk adolescents will provide further insight into the disease of addiction.

One of the most studied neurological risk markers for SUD is the P300 event-related potential (ERP). ERPs are electroencephalogram (EEG) voltage changes in response to events or stimuli from sensory, motor, or cognitive input. The P300 ERP is named for the positive voltage deflection read by electrodes over the parietal lobe, with a latency (delay between stimulus and response) of 300–600 ms. The more attention the patient gives to the stimulus, the stronger the P300 ERP will be recorded. Initially, research found that the P300 ERP was diminished in children of alcoholics, and that a reduced P300 was a predictor of later alcohol abuse [32]. Further research suggested that a reduced P300 ERP was more strongly correlated with conduct disorder and overall trait disinhibition [33], as defined by impulsivity and externalizing behavior, though it must be noted that even this research is viewed as controversial. So, while P300 may not be a specific predictor of SUD, it may serve as a useful and interesting physiological marker of disinhibition, one of the main risk factors for SUD.

In high-risk children (from families with significant alcohol dependence), fMRI studies suggest poor frontal functioning even before drug use began, and this impaired frontal function can predict later substance use [34].

Serotonin and Dopamine

Endogenous serotonin (5-HT) levels have been studied as a risk factor for substance use, given previous research suggesting that serotonin dampens the impact of dopamine in our reward-seeking behavior. Because it is difficult to measure the levels of 5-HT in the brain, researchers have used peripheral markers, including platelet 5-HT, whole blood 5-HT concentration, or platelet MAO (monoamine oxidase) activity. In children of alcoholics, lower whole-blood 5-HT was correlated with more externalizing behavior [35]. Higher platelet 5-HT concentrations were associated with greater
impulsivity [36], and certain 5-HT transporter polymorphisms [37] and transporter gene combinations [38] appear to increase the risk for SUD. However, like the P300 ERP, 5-HT dysfunction is more strongly correlated with disinhibition than with SUD [12].

Dopamine receptors have shown some genetic variability linked with SUD development. In children of addicts, the A1 allele of the D2 receptor (DRD2) was linked to higher rates of SUD [39]. The A1 allele is thought to result in reduced dopamine binding and lower D2 receptor expression [40]. However, the A1 allele has also been linked to antisocial behavior and negative affect [12], and to date no studies have controlled for these covariables. It is possible, and indeed probable, that the A1 DRD2 allele is a non-specific risk factor for disinhibition in general.

The Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis has a central role in much of our emotional life, and it is not surprising that it is an important player in the neurobiology of substance abuse. In response to stress, HPA axis activation results in the release of cortisol, which has been shown to enhance dopamine release from the VTA into the ventral striatum, like addictive drugs [41]. High-risk children of addicts have a blunted cortisol response to stress, and also have higher levels of impulsivity and externalizing behavior [42]. The level of cortisol response was negatively related to levels of externalizing behavior, and this relationship was stronger in adolescent girls than boys [43]. Thus, externalizing behavior, SUD, and a hypoactive HPA axis are all linked together. However, this finding is not consistent with other studies, which have identified a link between a hyperactive HPA axis, elevated cortisol response, internalizing disorders like depression and anxiety, and SUD [44]. Therefore, both HPA hyperactivity and hypoactivity pose a risk for SUD, most likely mediated by the hypoactive response to stress in the externalizing disorders (antisocial, conduct) and the hyperactive response to stress in the internalizing (anxious, depressed). Taken together, these findings indicate the complicated nature of substance use disorders, and the multiple pathways that can lead to substance abuse.

THE NEUROTOXIC IMPACT OF ALCOHOL AND MARIJUANA

Next, we move on to a discussion about the biological impact of illicit substances on the adolescent brain. Because research on the neurotoxic effects of drugs on the adolescent brain is ethically challenging, we have focused our discussion on the available literature surrounding abuse of alcohol and marijuana, the two drugs most commonly abused by adolescents.

Alcohol
Alcohol is the most abused drug in adolescence, and it is the most studied, with the majority of research done with animals, for obvious ethical reasons. Adolescents appear to be less sensitive than adults to alcohol’s behavioral effects, at least in rats. Spear [45] has shown that adolescent rats are less affected than adult rats by the social, motor, sedation, acute withdrawal, and “hangover effects” of ethanol. However, alcohol may be more toxic to the adolescent brain. Adolescent rat brains exposed to ethanol show less neural growth in the hippocampus, and those adolescent rats have worse hippocampal-dependent memory problems [46]. In human imaging studies, alcohol-abusing adolescents were compared with healthy peers and were found to have smaller frontal and hippocampal volumes, altered white matter microstructure, and poorer memory. The hippocampus was smaller in patients who began drinking earlier and who used for longer. Alcohol-using adolescents show altered anisotropy in the corpus callosum, and in adolescent binge drinkers, the frontal, cerebellar, temporal, and parietal regions all showed altered anisotropy. Heavy drinking is associated with diminished frontal cortex activation during spatial working memory tasks, as well as neuropsychological tests of attention, memory retrieval, and visuospatial functioning [5,47]. In longer-term follow-up studies, Squeglia identified gender differences. Girls who drank more often had a greater loss in visuospatial functioning. Alcohol-abusing girls had smaller PFC volumes than controls, while their male counterparts had larger PFC volumes than controls. Girls may be more sensitive than boys to the neurotoxic effects of alcohol: alcohol-abusing girls had a decreased frontal response to spatial working memory and reduced gray matter in comparison to alcohol-abusing boys [1,48].

Marijuana

In studies using fMRI, adolescent marijuana users have less efficient activation in working memory, verbal learning, and cognitive control tasks. Studies consistently show use of alternate brain networks in marijuana-using adolescents [1]. Smokers have larger cerebellar volumes, and female smokers have larger prefrontal cortex volumes than female non-smokers, with both findings suggestive of impaired synaptic pruning [49]. White matter integrity is worse in fronto-parietal and fronto-temporal circuits [50], and as a corollary, adolescent marijuana smokers are at greater risk for depression, and have worse performance on psychomotor speed, complex attention, verbal memory, planning and sequencing ability, even after a month-long abstinence [51].

CONCLUSION

The study of adolescent brain development and the changes that predispose it to risk-taking behaviors such as substance abuse is a fast-changing landscape. Ultimately, a theoretical construct that will likely withstand the test of time will include an “accelerator” currently thought to be
located in the ventral striatum and a “brake” currently thought to be a part of the prefrontal cortex. The overall balance and development of these two opposing forces will likely govern the behavioral phenotypes observed in adolescents as they transition into young adulthood. Current thoughts on this subject include the idea that our somewhat arbitrary cut-off definitions for adolescence may not accurately represent neurodevelopmental changes related to risk-taking behavior. In fact, when actuarial data are taken into consideration (as is most frequently done by car-rental and insurance companies) the time period to stability in impulse-control/modulation most likely occurs in the mid-20s. Interestingly, this is when car insurance rates begin to decline for most drivers and when young adults are actually allowed to rent cars. As we begin to understand more about our brains and the manner in which they develop, we will continue to improve our understanding of modulating risk-taking behavior.

References


