

Developmental Neurocircuitry of Motivation in Adolescence: A Critical Period of Addiction Vulnerability

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Objective: Epidemiological studies indicate that experimentation with addictive drugs and onset of addictive disorders is primarily concentrated in adolescence and young adulthood. The authors describe basic and clinical data supporting adolescent neurodevelopment as a biologically critical period of greater vulnerability for experimentation with substances and acquisition of substance use disorders.

Method: The authors reviewed recent literature regarding neurocircuitry underlying motivation, impulsivity, and addiction, with a focus on studies investigating adolescent neurodevelopment.

Results: Adolescent neurodevelopment occurs in brain regions associated with

motivation, impulsivity, and addiction. Adolescent impulsivity and/or novelty seeking as a transitional trait behavior can be explained in part by maturational changes in frontal cortical and subcortical monoaminergic systems. These developmental processes may advantageously promote learning drives for adaptation to adult roles but may also confer greater vulnerability to the addictive actions of drugs.

Conclusions: An exploration of developmental changes in neurocircuitry involved in impulse control has significant implications for understanding adolescent behavior, addiction vulnerability, and the prevention of addiction in adolescence and adulthood.

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Substance use disorders are a leading cause of medical morbidity, mortality, and health expenditures in the United States (1). Regional availability of substances and social trends influence the prevalence of specific substance use disorders (2). Three major observations suggest that the developmental periods of adolescence and early adulthood are primary correlates of substance use and substance use disorders, operating across cultural trends and substances. First, adolescents and young adults generally exhibit higher rates of experimental use and substance use disorders than older adults, as indicated by studies of the general population spanning the last two decades and with the use of alternate diagnostic criteria (3–5). Second, addictive disorders identified in adults most commonly have onset in adolescence or young adulthood (6, 7). For example, most adult U.S. smokers begin smoking before age 18 (8), and the onset of daily smoking is uncommon after age 25 (9). Over 40% of adult alcoholics experience alcoholism-related symptoms between ages 15 and 19, and 80% of all cases of alcoholism begin before age 30 (10). The median reported age of initiation of illicit drug use in adults with substance use disorders is 16 years, with 50% of cases beginning between ages 15 and 18 and rare initiation after age 20 (3). Third, earlier onset of substance use predicts greater addiction severity and morbidity, including use of—and substance use disorders associated with—multiple substances (6, 11, 12). Although

epidemiological surveys generally show greater prevalence of substance use disorders in male than in female subjects across ages, these age-specific trends are observed in both male and female subgroups, suggesting the existence of gender-independent factors in the developmental onset of substance use disorders (4, 13).

Two key variables in the genesis of addictive disorders are the 1) degree/amount of drug intake and 2) the inherent vulnerability to addiction given a fixed amount of drug intake (14, 15). Understanding whether one or both of these factors are greater in adolescence is important in explaining the developmental onset of substance use disorders. Although cultural, peer, and family influences contribute to drug availability and substance experimentation (16), several lines of evidence suggest that sociocultural aspects particular to adolescent life alone do not fully account for greater drug intake. Although marketing and the availability of legal drugs (alcohol and nicotine) are pervasive across age groups in American society and are legally sanctioned only for adults, the onset of substance use disorders associated with these drugs is concentrated in adolescence and young adulthood and does not increase in a cumulative manner with increasing age. In Europe, where teen cultural norms and societal limitations regarding substances vary from those in the United States, the incidence and morbidity associated with substance

use disorders similarly occur frequently in adolescents and young adults (17, 18).

Genetic and neurobiological factors within individuals are thought to lower the threshold of drug exposure required for “tripping the switch” from experimental to addictive drug use (15). Growing clinical evidence suggests that adolescence represents a period of heightened biological vulnerability to the addictive properties of illegal and legally sanctioned substances. For instance, adolescents demonstrate a more precipitous progression of illicit drug use than adults (4, 19). Despite smoking fewer cigarettes than adults, adolescents show higher rates of dependence at similar levels of use (20), and although rates of alcohol use are similar throughout adolescence and adulthood, rates of abuse/dependence vary inversely with age (5). This article reviews basic and clinical evidence for adolescent neurodevelopment as a critical period of addiction vulnerability. Behaviors seemingly characterized by impulsivity and suboptimal decision making are described as normative traits of adolescence corresponding to the development of motivational circuitry involved in the pathophysiology of addiction. Developmental events that facilitate motivational drives promoting learning about adult experiences may simultaneously increase vulnerability to neurobehavioral effects of addictive drugs, leading to substance use disorders.

Impulsivity and Decision Making

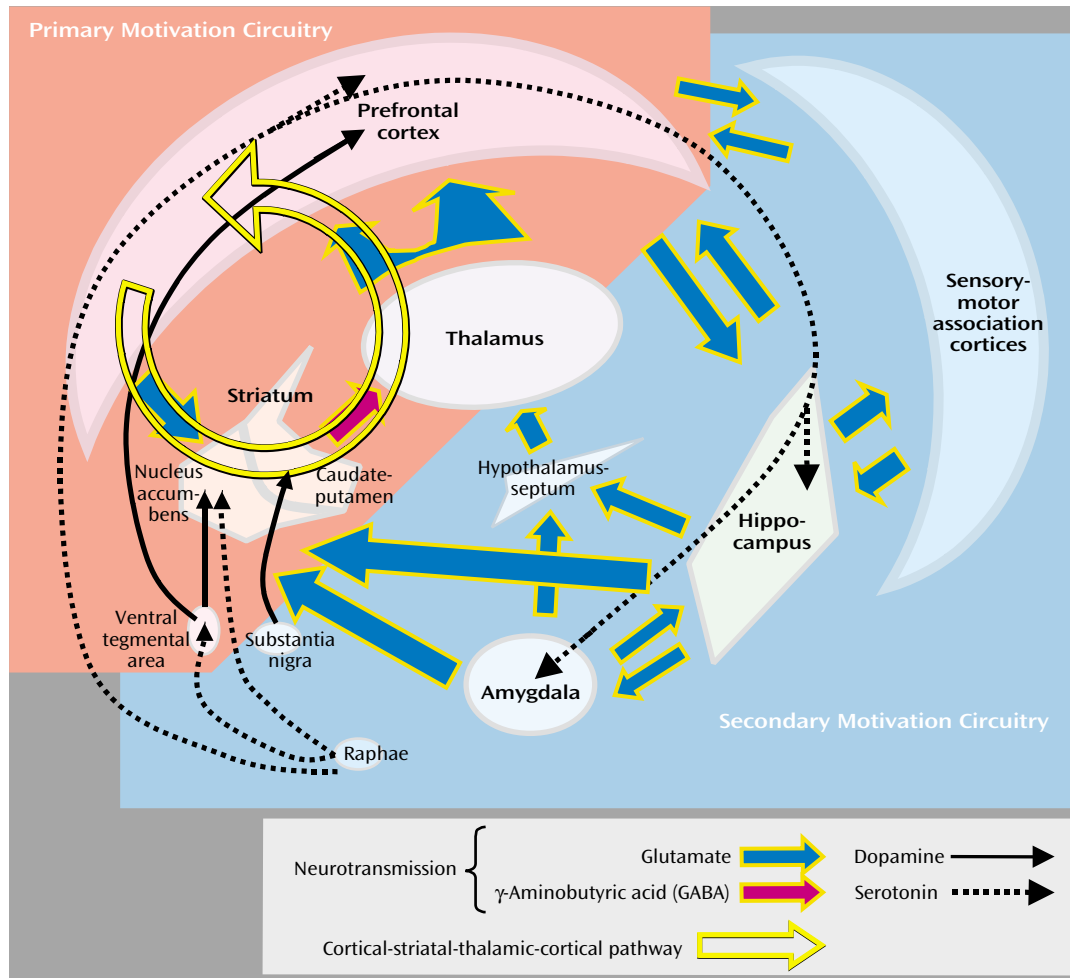
The prevalence of substance use disorders is elevated in adults with schizophrenia, major affective disorders, antisocial and borderline personality disorders, and pathological gambling (2, 3, 10, 21, 22). Adolescents with antecedent or fully expressed versions of these disorders are also more likely to have substance use disorders (23–25). Associations of these mental illnesses and adolescence with substance use disorders suggest that common brain mechanisms may underlie vulnerability to substance use disorders in these different contexts. These mechanisms might manifest as a general clinical motif or behavioral trait that transcends adolescent, psychiatric, or substance use disorder groups. Impaired impulse control represents one such motif (23, 26, 27). As with other descriptive constructs in clinical psychiatry, the precise meaning of impulsivity and its relationship to traits of novelty or sensation seeking are debatable. Varieties of impulsivity have been proposed, depending on the clinical measure and the function of specific brain regions being assessed (28). Here we formulate impulsivity as goal-directed behavior characterized by poor judgment in the attainment of rewards, such as addictive drugs, sex, food, social power (by means of violence), money, or other resources (27, 28). With this definition, impulsive behaviors generally lead to disadvantageous or deleterious consequences; behaviors characterized by increased novelty seeking or poor decision making may be considered impulsive (29).

Psychiatric disorders commonly identified with disturbances in reward motivation and substance use disorder comorbidity are associated with impulsivity (3, 27, 28, 30). Instruments measuring decision making identify impulsivity as a preference for high-risk/low-benefit choices or lesser immediate rewards over greater delayed rewards (temporal discounting) (31, 32). Impulsive response patterns have been identified in association with impulse-control disorders, substance use disorders, and psychiatric diagnoses with impulse-control disorder and/or substance use disorder comorbidity (26, 33). Although similar instruments have not yet been applied in adolescents, impulsivity and/or novelty seeking are generally observed to increase in adolescence and decline with age (34, 35).

Understanding the relationship between impulsivity and substance use disorders may prove important to understanding the pathogenesis of substance use disorders and their greater prevalence in specific clinical contexts, including adolescence. Conceptualizations of the clinical syndromes of substance use disorders and poor impulse control or decision making share features suggesting similar forms of motivational psychopathology. Individuals with poor impulse control show a thematic tendency to engage in behaviors characterized by long-term disadvantageous outcomes. Similarly, addictive substances are collectively associated with chemical stimulation and neuroplastic changes in brain motivation substrates, leading to further drug use at the expense of social and occupational outcomes (15). Analogous clinical conceptualizations of impulsivity and addictions in terms of dysfunctional motivational repertoires may reflect common neurobiological mechanisms involving motivational neurocircuitry.

Neurocircuitry of Motivational Substrates

Understanding the anatomy and function of motivational brain systems may provide important information about correspondences between impulsivity, risk for substance use disorders, and adolescence. Motivation can be conceptualized as brain activity that processes “input” information about the internal state of the individual and external environment and determines behavioral “output” (36). Rather than operating as a simple reflex system producing discrete behaviors in response to discrete stimuli, motivation involves higher-order processing designed to organize behavior to maximize survival (37). Goal-directed behavior involves integrating information about multiple changing internal states (e.g., hunger, sexual desire, or pain) and environmental conditions (including resource or reproductive opportunities, the presence of danger) in generating an advantageous behavioral response (31). Compounding this complexity, multiple survival goals may be simultaneously important but independently attainable in space and time, and there may exist large numbers of potentially successful behavioral strate-

FIGURE 1. Major Motivational Brain Circuitry Putatively Involved in Impulsivity, Decision Making, and Drug Addiction^a

^a Primary motivation circuitry directly subserves the neurocomputational events of decision making and the selection of motivational drives for behavioral action. These events are determined by subsystems integral to cortical-striatal-thalamic-cortical pathways (open yellow arrow) that can either promote or inhibit the enactment of motivated drives. Secondary motivation circuitry provides the input (affective, memory, sensory, hormonal/homeostatic information) that generates and influences the fate of motivational drives in primary motivation circuitry. Addictive drugs, primarily by virtue of neuroplastic changes associated with dopamine activity most highly concentrated in primary motivation circuitry, produce long-term motivational effects.

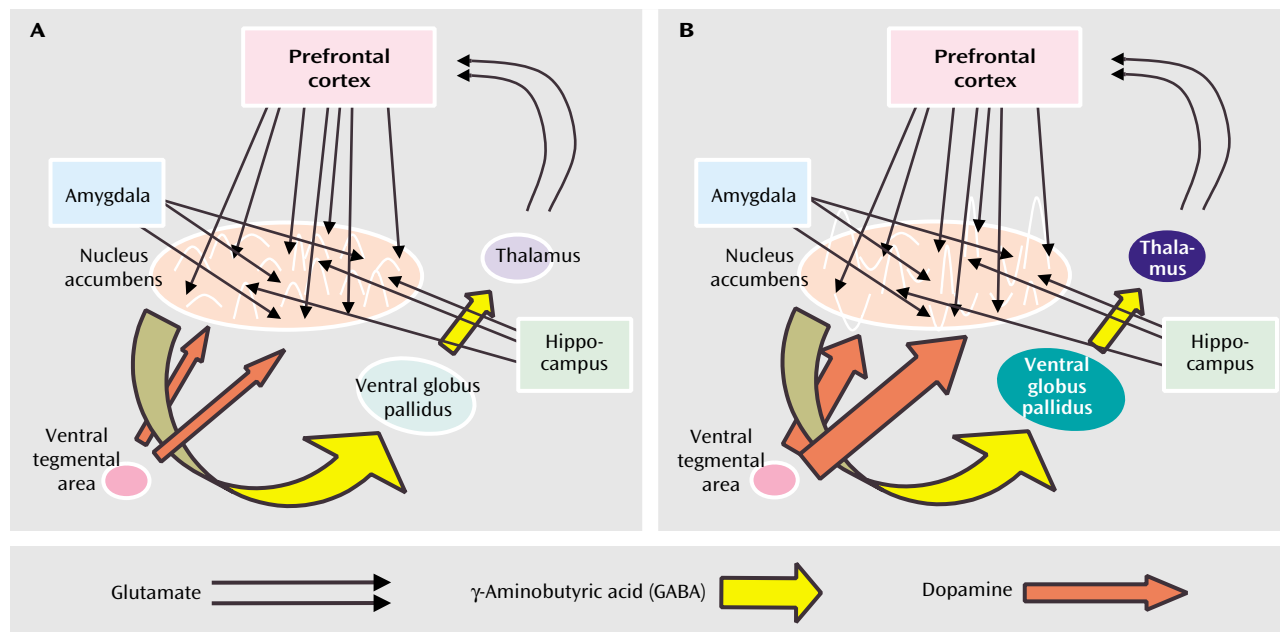
gies to attain one or more of these goals. Motivational neurocircuitry should therefore involve mechanisms capable of representing alternative motivated drives and efficiently prioritizing and selecting appropriate motivated drives for enactment (36, 38).

Translational neuroscience is beginning to generate neurobiological evidence supporting these theoretical considerations. The importance of motivation to evolutionary fitness would predict that substantial portions of the brain are involved, following a hierarchical anatomical and functional organization conserved across species. Animal and human studies suggest the existence of a primary motivation circuitry involving the prefrontal cortex and ventral striatum, which has direct access to and influence on motor "output" structures (37). This anterior system is supported by a more widely distributed and posteriorly situated secondary motivation circuitry that provides

multiple modalities of sensory "input" information by means of direct axonal projections converging into primary motivation circuits (Figure 1) (39–41). For example, the hippocampus and amygdala provide contextual memory and affective information relevant to motivational stimuli (31, 39, 42, 43), while hypothalamic and septal nuclei provide information relevant to primitive or instinctual motivated behaviors, such as nutrient ingestion, aggression, and reproductive responses (44).

Recent findings characterize primary motivation circuitry as containing populations of neurons capable of generating firing patterns that may encode multiple aspects of motivated drives or alternative motivated drives (45). These representations occur among neuronal ensembles interconnected by parallel loops of serial axonal projections from the prefrontal cortex to the ventral striatum (the nucleus accumbens to the ventral globus palli-

FIGURE 2. Cortical-Striatal-Thalamic-Cortical Loops Within Primary Motivation Circuitry Involved in the Representation of Motivated Drives and the Neurocomputational Events of Motivational Decision Making and Behavioral Instigation^a



^a Part A shows that glutamatergic afferents from the prefrontal cortex, in conjunction with those from the amygdala and hippocampus, convey executive, affective, and contextual memory information to the nucleus accumbens by influencing the firing patterns of neuronal ensembles in the nucleus accumbens, depicted as local peaks in firing rates. Nucleus accumbens architecture allows a vast number of motivational possibilities to be represented by a corresponding diversity of firing patterns. Motivational information is conveyed by GABA-ergic afferents to the ventral globus pallidus and then to the thalamus, which in turn influence cortical and subcortical centers of motor output. Part B shows that dopamine discharge in the nucleus accumbens (thickened red arrows) is implicated in the identification of environmental novelty, the actions of addictive drugs, and the gating of motivated drives into behavioral actions by changing responses of nucleus accumbens neurons to cortical and limbic glutamatergic afferents. These events are proposed to lead to relative extremes in firing patterns among nucleus accumbens neuronal ensembles, depicted as increases in local peak amplitudes that code for behaviorally activating events in downstream motor systems. These events may also facilitate mechanisms of neuroplasticity among nucleus accumbens neurons and their afferents, determining the future repertoire of motivational drive representations and/or thresholds for behavioral instigation. During adolescence, ongoing frontal cortical maturation (limiting motivational inhibitory capacity), along with robust novelty-encoding dopamine activity, may enhance the action of addictive drugs to cause the system to operate in a promotional motivated state (as in B), producing more profound long-term motivational consequences.

dus) to the thalamus and back to the cortex (46, 47) (Figure 1 and Figure 2). Cortical-striatal-thalamic-cortical loops are described as parallel because specific subregions of the prefrontal cortex (e.g., anterior cingulate, ventromedial, and dorsolateral regions) project to specific compartments within the striatum, which in turn maintain some degree of segregation in projections to the thalamus and back to the cortex (48). Both anatomical and neurophysiological evidence suggest that firing patterns of neuronal ensembles within functionally specific compartments of the striatum are in part correlated with patterns of firing in specific prefrontal cortex subregions (42, 49). In turn, firing patterns in both the nucleus accumbens and prefrontal cortex are influenced by glutamatergic inputs from the hippocampus and amygdala, suggesting that abnormalities in these distal structures may produce both mental illness and motivational disorders (50). Because striatal populations have direct influence on premotor and motor cortices and brainstem motor centers, their activity more directly determines motivational states and behavioral output (39, 44). Dense collections of γ -aminobutyric acid

(GABA)-ergic inhibitory neurons in the striatum communicate by means of recurrent collateral inhibition that is suggestive of the high capacity of local neural networks to encode vast numbers of alternative firing patterns that could serve as computational building blocks of multiple, highly elaborated motivated drives (39, 47, 51–67).

Accumulating evidence suggests that neurocircuitry encoding repertoires of alternative motivated drives are subject to neurobiological events that prioritize and select motivated drives for behavioral action. Particular neural substrates have been associated with promoting (increasing the probability of enactment) or inhibiting motivated drives. Disturbances of motivational repertoire, including varieties of impulsivity and addictions, may thus commonly reflect poor coordination or abnormal functioning of promotional or inhibitory neural systems integral to primary motivation circuitry (41, 52). Consistent with this notion, neuroimaging studies implicate common subcortical-striatal regions and the prefrontal cortex in emotional and cognitive processes of decision making and the pharmacological action of addictive drugs (53). To further

explore this hypothesis, data characterizing promotional and inhibitory motivation substrates will be described, followed by a review of changes within these pathways during adolescence.

Promotional Motivation Substrates

Dopamine release into the striatum is a principal neuromodulatory event implicated in the translation of encoded motivated drives into action, operating like a general "go" signal (54). Dopamine release into the ventral striatum (nucleus accumbens) and dorsal striatum (caudate putamen) is provoked by excitatory signals from the cortex and other areas that stimulate dopamine neuron activity in the ventral tegmental area and substantia nigra, respectively (55, 56) (Figure 1). However, the ventral and dorsal sections are associated with different levels of premotor processing. Dopamine release into the dorsal striatum, compromised in the pathogenesis of Parkinson's disease, is primarily associated with the initiation and flow of concrete motor activity and habitual behavior (57). In contrast, dopamine release into the nucleus accumbens is associated with motivational stimuli, subjective reward, premotor cognition (thought), and learning of new behaviors (43, 46, 58). The precise manner in which dopamine release is involved in the translation of thought into action is unknown. Some work indicates that dopamine discharge directly affects the firing patterns of neuronal ensembles in the nucleus accumbens and influences their responses to glutamatergic input from the cortex, amygdala, and hippocampus (51, 59) (Figure 2B). This finding suggests that sensory, affective, and contextual memory information, leading to the generation of representations of motivated drives, is gated by dopamine release in the striatum, such that downstream motor centers can receive and act upon specific motivational information (51, 59, 60). Accordingly, neurotoxic lesions of the prefrontal cortex, amygdala, or hippocampus alter behavioral repertoires provoked by pharmacological stimulation of dopamine release in the nucleus accumbens (61–63).

A wide variety of motivational stimuli have been shown to increase dopamine in the nucleus accumbens. These include the pharmacological actions of addictive drugs (including nicotine, alcohol, cocaine, amphetamine, opiates, cannabis), natural rewards (food, sex, or other resources), reward-related stimuli and situations (video-game playing), and stressful or aversive stimuli (43, 64–67). Environmental awareness is vital for the efficient acquisition of reward resources, and the drive to seek and explore the unknown is itself a powerful primary motivation (43). Environmental novelty provokes ventral-striatal dopamine release (68) and, like addictive drugs, produces locomotor behavior in laboratory animals (69). Novelty, presented in the form of unpredicted contingencies or environmental stimuli, in combination with addictive drugs, is particularly motivating (70). Rewards delivered in intermittent, random, or unexpected fashions have greater ca-

capacity over repeated trials to maintain dopamine cell firing and reward-conditioned behavior (71, 72). In contrast, many well-learned motivated behaviors or habits performed under expected contingencies become less dependent on nucleus accumbens dopamine release. Thus, direct pharmacological stimulation of dopamine systems mediated by addictive drugs appears to mimic and/or act synergistically with the natural motivational-encoding properties of environmental novelty.

A second important function of dopamine, together with glutamatergic afferent activity in the nucleus accumbens and intrinsic GABA-ergic activity of nucleus accumbens neurons, involves the determination of future representations and selection preferences of motivated drives. In reward-related learning, future behavior is shaped according to past experiences associated with rewards by means of neuroplastic changes in nucleus accumbens neurons (73). Repeated drug-provoked dopamine release in the nucleus accumbens induces changes in cellular proteins involved in intracellular receptor signaling pathways, gene expression, and cellular architecture (15). Dopamine transmission in nucleus accumbens and prefrontal cortex regions projecting to the nucleus accumbens has been implicated in mechanisms of learning and plasticity, including changes in long-term potentiation and morphology of neuronal dendritic trees (74–77). These neuroplastic processes may underlie behavioral sensitization, whereby the motivational drive associated with a reward becomes increasingly stronger as that reward context is repeatedly experienced (78, 79). Sensitization, as an increase in the motivational priority associated with a particular contextual reward relative to other encoded motivational drives, produces reward-specific acquisition behavior that becomes increasingly compulsive (78). In this manner, dopamine systems activity may serve a long-term function of narrowing or focusing the repertoire of motivational drives of the individual.

Inhibitory Motivation Substrates

Deficiencies of function or structure of inhibitory systems are associated with the enactment of motivated drives deemed suboptimal or inappropriate. Chief among these are the serotonin (5-HT) neurotransmitter system and prefrontal cortex components of motivational circuitry (Figure 1). Measures of decreased brain 5-HT activity are associated with impulsive behaviors, including outward and self-directed violence, suicide, fire starting, and pathological gambling (80–82). Pharmacological injury of 5-HT systems in animals results in impulsive responding in reward-related learning and incentive motivation (83). Conversely, pro-serotonergic agents decrease social aggression and impulsivity in animals and humans (84, 85). Although mechanisms for these findings have not been fully elaborated, 5-HT projections from the midbrain raphe nuclei to motivational circuitry, including the ven-

tral tegmental area, nucleus accumbens, prefrontal cortex, amygdala, and hippocampus, appear involved (55, 86).

Prefrontal cortex function has long been associated with impulse control. Documented as early as 1848, damage to the ventromedial prefrontal cortex causes pervasive motivational impulsivity associated with affective instability, poor decision making and executive planning, and indifference to social cues (87). Impaired impulse control has subsequently been reported in numerous neuropsychiatric conditions (e.g., antisocial personality disorder, affective disorders, schizophrenia, substance use disorders, dementias, and traumatic brain injury) characterized by abnormal measures of prefrontal cortex function (26, 30, 88–90).

Prefrontal cortex abnormalities are associated with a greater risk of developing substance use disorders, possibly involving changes in motivational responses to addictive drugs. Clinical studies demonstrate an association of traumatic brain injury, often involving the prefrontal cortex, with heightened substance use disorder comorbidity and suggest that the onset of either of these factors alone increases risk for the other (91–93). Functional or anatomical abnormalities of the prefrontal cortex of nonspecific etiology are also commonly identified in populations with substance use disorders (94–97). Corresponding to these clinical observations, prefrontal cortex lesions in rats can augment the reinforcing efficacy of cocaine during self-administration (98, 99).

Investigations of corticostriatal interactions suggest a mechanism for prefrontal cortex dysfunction, producing both impulsivity and greater risk for substance use disorders. Excitatory glutamatergic projections from the prefrontal cortex to the nucleus accumbens and ventral tegmental area influence dopamine release, neuronal firing, and neuroplastic processes in the nucleus accumbens (39, 100, 101). These anatomical and functional linkages suggest that the prefrontal cortex is involved in the representation, execution, and inhibition of motivational drives by influencing patterns of neural ensemble firing in the nucleus accumbens. Compromise of the prefrontal cortex or its inputs to the nucleus accumbens could 1) alter the variety of representations of motivational drive options in the nucleus accumbens, 2) alter the response patterns across nucleus accumbens neuronal ensembles to the “go” signal provided by dopamine influx, resulting in greater probability of enactment of particular motivated drives, and/or 3) impair neuroplastic processes in the nucleus accumbens that would normally decrease the strength of motivated drives deemed inappropriate by prior experience. Poor prefrontal cortex function, regardless of the specific pathology, could increase the probability of performing inappropriate motivated drives viewed clinically as impulsive. Similarly, prefrontal cortex dysfunction may result in 1) preferential motivational responding to directly encoded rewards provided by the prodopamine effects of drugs and/or 2) an unchecked

progression of neuroadaptive effects of drugs underlying motivational sensitization and a switch to compulsive drug seeking (102, 103). As such, relative impairment of inhibitory motivational systems in the setting of robust promotional motivation systems activity would commonly increase impulsivity and the risk of substance use disorders. Neurodevelopmental changes during adolescence leading to these conditions could generate heightened addiction vulnerability.

Maturation of Motivational Neurocircuitry During Adolescence

Profound psychophysiological change occurs during adolescence. Adolescents acquire increasingly adult-like cognitive and emotional styles (104, 105) and become increasingly motivated by adult environmental stimuli (106). In childhood, motivation to play promotes nonparticipatory learning about adult experiences, a process that minimizes damaging outcomes (43). In adolescence, motivation to play progresses to participation in novel adult experiences, without the benefits of contextual experiential knowledge to guide decision making (107). From an adult perspective, novelty-driven adolescent behavior may seem of poor judgment and impulsive (34, 35).

Promotional Motivation Substrates

Developmental alterations in primary motivation circuitry during adolescence may promote novelty-seeking behavior and augment incentive motivational processes. Neuropsychiatric disorders involving central dopamine function follow developmental patterns consistent with this notion. Tic disorders, treated by blocking dopamine activity, are most prevalent in late childhood and early adolescence and tend to remit in adulthood (108). In contrast, the incidence of Parkinson's disease, involving deficient dopamine function, increases with advancing age (57). That these observations reflect general developmental themes is supported by animal studies showing differences in peri-adolescent behavior involving dopamine systems function (109). Peri-adolescent rats show heightened exploratory behavior in a novel open field and engage more in social play than younger and older rats (110). Peri-adolescent rats show motoric hyporesponsivity to prodopaminergic agents and hypersensitivity to dopamine blockade, suggesting that their dopamine system operates at baseline closer to a functional ceiling before pharmacological challenge (110). Peri-adolescent mice show a greater baseline preference for novel environments than adult mice (111). Upon amphetamine treatment, adults show increases in novelty preferences and peri-adolescents exhibit decreases, preferring instead the familiar environment previously paired with amphetamine delivery (111). Peri-adolescent rats show greater behavioral sensitization and striatal dopamine release after repeated psychostimulant injections than adult rats (112,

113). Together, these findings suggest that adolescent experimentation with and vulnerability to addictive drugs involve developmental differences in dopamine system activity and sensitization.

Maturational differences in promotivational dopamine systems and inhibitory 5-HT systems may contribute to adolescent novelty seeking/impulsivity. CSF concentrations of dopamine and 5-HT metabolites decline during childhood and decrease to near adult levels by age 16 (114). However, the ratio of the dopamine metabolite homovanillic acid to the 5-HT metabolite 5-hydroxyindoleacetic acid increases, suggesting a higher rate of dopamine to 5-HT turnover (114). In monkeys, the density of dopamine-bearing presynaptic endings in the prefrontal cortex increases from one-half of adult levels at 6 months of age to adult levels by late adolescence (2 years), when the density of dopamine axonal input is approximately threefold that of 5-HT (115). In contrast, 5-HT production sites on prefrontal cortex neurons reach adult levels by the second week after birth (115). Together, these findings indicate that adolescence may be characterized by greater activity in promotivational dopamine systems than in inhibitory 5-HT systems.

Adolescent hormonal changes affecting secondary motivation circuitry may also contribute to promotivational functioning of dopamine systems. Sex steroid receptors mediating profound neuroplastic effects are highly expressed in the hippocampus and the hypothalamus (116, 117). Neuroplastic revision during puberty may alter representations of contextual motivational stimuli in these structures, changing the nature of motivational drives represented in primary motivation circuitry (118, 119). For example, surges in sex hormones contribute to greater sexual motivation, sensitivity to novel sexual and social stimuli, sexual competition, and adolescent aggression (43, 120, 121).

Hippocampal function may be important to sex-hormone-related changes in novelty-oriented behavior. By means of broad connectivity with the cortex, the hippocampus compares immediate environmental contexts with past memories to detect environmental novelty (122). Resultant information can become encoded in motivational drives by means of hippocampal regulation of the amplitude or impact of dopamine discharge into the nucleus accumbens or by direct influences on neuronal activity of the nucleus accumbens (51, 123, 124). This notion is consistent with anatomical and physiological data showing that hippocampal damage alters quantitative dopamine release into the nucleus accumbens and behavioral responses to novel environments (69). Together, these data suggest a mechanism by which hormonal conditions in specific stages of life (childhood, adolescence, adulthood) may influence promotivational dopamine systems to orient behavior most adaptive to the developmental stage.

Inhibitory Motivation Substrates

Changes in promotional motivation substrates occur concurrently with developmental events in the prefrontal cortex. In adolescence, the prefrontal cortex has not yet maximized a variety of cognitive functions that may include its capacity to inhibit impulses. Measures of prefrontal cortex function, including working memory, complex problem solving, abstract thinking, and sustained logical thinking, improve markedly during adolescence (104, 105, 125). Although the ability to inhibit psychomotor responses improves through childhood, peaking by late adolescence (126), more direct measures of adolescent impulsivity (e.g., decision making) remain largely unexplored.

Changes in brain anatomy and function correspond temporally to changes in cognitive function. Throughout adolescence, changes in EEG measures of cortical activity and responses to sensory stimuli are observed (104, 127). From ages 6 to 12, the ratio of lateral ventricle to brain volume remains constant; it then increases steadily from ages 12 to 18 (128). From ages 4 to 17, there is a progressive increase in white matter density in the frontal cortex, likely due to increased myelination of neurons and axonal diameters and contributing to increased efficiency of action potential propagation (129). Changes in brain metabolism reflecting altered neuroplasticity and information processing are also observed. Globally, the brain increases energy use, matching adult levels by age 2, increasing to two-fold greater than adult levels by age 9, and declining to adult levels by the end of adolescence (130, 131). Compared to subcortical regions, cortical areas undergo similar but more pronounced temporal fluctuations of metabolic rates and exhibit these changes later, with frontal cortical regions transitioning last (131).

Gross developmental changes in the prefrontal cortex are paralleled by neuroplastic changes, as shown by densities of dendritic processes, synapses, and myelination, rates of neuronal membrane synthesis, and emergence of adult cognitive styles (129, 132–134). Declines in metabolic activity in frontal and other cortical regions may reflect synaptic pruning, whereby reductions are made in energy-consuming neuronal connections that do not efficiently transmit information pertaining to accumulating experience. In the human prefrontal cortex, synaptic density in major axonal reception zones increases to 17×10^8 per mm^3 between the ages of 1 and 5 and declines to adult levels of 11×10^8 per mm^3 by late adolescence (135). Synaptic pruning in peri-adolescent monkeys occurs in components of cortical microarchitecture indicative of specific effects on information processing (134). Reductions in prefrontal cortex synapses are greater for those of axons originating from local cortical regions rather than from distant association cortices and are proposed to reflect a relative increase in the reliance of local prefrontal cortex circuits on highly processed multimodal information (125). This feature may allow top-down processing, whereby a larger,

more sophisticated repertoire of past experience stored in distant structures has greater computational influence (134). Peri-adolescent synaptic pruning decreases both excitatory and inhibitory inputs (136). These counterbalanced reductions may increase the stability of firing patterns of cortical neurons (137) and enhance the capacity for ensembles of prefrontal cortex neurons to fire in a sustained, concerted fashion (134, 138), facilitating short-term storage of an increasing amount of information. Consistent with this notion, improved working memory performance in adolescent monkeys corresponds positively with the percentage of prefrontal cortex neurons showing sustained activity during the task's delay period (139).

Neural network simulations suggest that the increase in cortical interconnectivity in childhood followed by a decline to adult levels over adolescence reflects optimization of learning potential, corresponding to decreases in rates of neuroplastic change (125, 140). These processes determine a tradeoff between the capacity to learn new information versus that to use and elaborate on previously learned information (140). As accumulating information is stored in connections within neural networks, learning rates, or the capacities for neuroplasticity as represented by the number of synaptic connections, should decrease, resulting in a system that operates to prevent loss of previously learned information (140). Synaptic pruning and other developmental processes in the prefrontal cortex, concomitant with greater motivational drives toward novel adult experiences, may work in combination to facilitate adolescent acquisition of an increasingly sophisticated cognitive and perceptual understanding of the environment. Maturation of the prefrontal cortex is thus facilitated by motivational drives to participate in novel adult-like experiences, eventually leading to experience-based motivation that guides the enactment of more "appropriate" decision making.

Conclusions

Adolescent neurodevelopment involves changes in brain organization and function characterized by relatively greater influence of promotional motivation substrates in the setting of immature inhibitory substrates. Greater motivational drives for novel experiences, coupled with an immature inhibitory control system, could predispose to performance of impulsive actions and risky behaviors, including experimentation with and abusive use of addictive drugs. Similarly, psychiatric illnesses commonly comorbid with substance use disorders often involve impulse dyscontrol putatively reflecting chronically deficient inhibitory and/or hyperactive promotional mechanisms of motivational neurocircuitry. In normal adolescence, motivational neurocircuitry undergoes a transitional phase resembling these conditions. Direct pharmacological-motivational effects of addictive drugs on dopamine systems may be accelerated during these devel-

opmental epochs, enhancing the progression or permanency of neural changes underlying addiction.

A major implication of this model is that substance use disorders constitute neurodevelopmental disorders. As such, research and treatment targeting adolescents and young adults may benefit all age groups with substance use disorders. Further characterization of specific components of motivational neurocircuitry undergoing adolescent neurodevelopment (including subcortical dopamine and prefrontal cortex and other associated substrates) may reveal discrete mechanisms involved in gender or mental-illness-related differences in vulnerability to substance use disorders. The impact of practices in child and adolescent psychopharmacology on the development of motivational neurocircuitry and risk for substance use disorders is virtually unexplored. Limited data exist, with the majority of information derived from reports of the use of psychostimulants for attention deficit hyperactivity disorder. Findings suggest protective effects against substance use disorders in specific diagnostic groups or subgroups and possibly none or detrimental effects in others (141–144).

Additional investigation is required to test the proposed mechanisms and implications of this model. Evidence for an association between impulsivity and risk for substance use disorders across clinical contexts, including adolescence and/or psychiatric disorders, is strong but mostly correlative. Coordinated research with a variety of approaches is needed to examine directly the suggested causal relationships. Animal models of impulsivity and addictive behavior in drug self-administration should be tested within subjects with both cross-sectional and longitudinal approaches. Genetic, molecular, neurochemical, and neurophysiological methods should be applied to these models to identify common and unique aspects of motivational circuitry predisposing to both impulsivity and addiction. Neurocomputational simulations of primary motivational circuitry, incorporating multiple lines of biological data, may be required to examine phenomena on a neural systems level not easily studied in unimodal biological investigations.

Given the proposed existence of brain mechanisms that commonly produce impulsivity and risk for substance use disorders in mental illnesses that also frequently appear in young adulthood, it remains to be determined to what extent adolescent vulnerability to substance use disorders 1) reflects the early manifestation of adult psychiatric syndromes that confer greater risk for substance use disorders and/or 2) represents a greater risk across all adolescent subgroups. Possibly both options occur, producing greater vulnerability for substance use disorders in all adolescents but to a greater degree in psychiatrically compromised youth. Such an interpretation would be consistent with the existence of individually unique genetic and environmental risk and protective factors working in conjunction with temporal developmental changes in brain

function to generate a specific level of addiction vulnerability. In assessing the relative contributions of these possibilities, animal modeling of substance use disorders in subjects during different developmental stages, with alternative schedules of peri-adolescent drug exposure, will be important, including the use of within-subjects animal models of mental illness and substance use disorders. Longitudinal clinical studies, particularly those employing objective measures of impulsivity and decision making and using genetic and functional neuroimaging technologies, will be of significant value in understanding addiction vulnerability across age groups in healthy and psychiatrically ill adolescents (31). The identification of adolescent subgroups with heightened vulnerability to substance use disorders, development of evidence-based preventative strategies, and refinement of pharmacotherapeutic and psychosocial treatments are important areas to pursue in order to reduce the large impact of substance use disorders upon society.

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References

- Gambling Impact and Behavior Study. Chicago, University of Chicago, National Opinion Research Center, 1999
- Bucholz KK: Nosology and epidemiology of addictive disorders and their comorbidity. *Addict Disord* 1999; 22:221-239
- Anthony J, Helzer J: Syndromes of drug abuse and dependence, in *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. Edited by Robins LN, Regier DA. New York, Free Press, 1991, pp 116-154
- Warner LA, Kessler RC, Hughes M, Anthony JC, Nelson CB: Prevalence and correlates of drug use and dependence in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1995; 52:219-229
- Grant BF: Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. *J Stud Alcohol* 1997; 58:464-473
- Kandel DB, Yamaguchi K, Chen K: Stages in progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *J Stud Alcohol* 1992; 53:447-457
- Wagner FA, Anthony JC: From first drug use to drug dependence: developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 2002; 26:479-488
- Giovino GA: Epidemiology of tobacco use among US adolescents. *Nicotine Tobacco Res Suppl* 1999; 1:S31-S40
- Breslau N, Johnson EO, Hiripi E, Kessler R: Nicotine dependence in the United States: prevalence, trends, and smoking persistence. *Arch Gen Psychiatry* 2001; 58:810-816
- Helzer JE, Burnam MA, McEvoy LT: Alcohol abuse and dependence, in *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. Edited by Robins LN, Regier DA. New York, Free Press, 1991, pp 81-115
- Taioli E, Wynder E: Effect of the age at which smoking began on frequency of smoking in adulthood. *N Engl J Med* 1991; 325:968-969
- Anthony JC, Petronis KR: Early-onset drug use and risk of later drug problems. *Drug Alcohol Depend* 1995; 40:9-15
- Kandel D, Chen K, Warner LA, Kessler RC, Grant B: Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the US population. *Drug Alcohol Depend* 1997; 44:11-29
- Carroll ME, Lac ST: Acquisition of IV amphetamine and cocaine self-administration in rats as a function of dose. *Psychopharmacology (Berl)* 1997; 129:206-214
- Nestler EJ, Barrot M, Self DW: Δ FosB: a sustained molecular switch for addiction. *Proc Natl Acad Sci USA* 2001; 98:11042-11046
- Trad PV: Developmental vicissitudes that promote drug abuse in adolescents. *Am J Drug Alcohol Abuse* 1994; 20:459-481
- Perkonig A, Lieb R, Wittchen HU: Prevalence of use, abuse and dependence of illicit drugs among adolescents and young adults in a community sample. *Eur Addict Res* 1998; 4:58-66
- Rehm J, Gmel G, Room R, Frick U: Average volume of alcohol consumption, drinking patterns and related burden of mortality in young people in established market economies of Europe. *Eur Addict Res* 2001; 7:148-151
- Estroff TW, Schwartz RH, Hoffman NG: Adolescent cocaine abuse: addictive potential, behavioral and psychiatric effects. *Clin Pediatr* 1989; 28:550-555
- Kandel DB, Chen K: Extent of smoking and nicotine dependence in the United States: 1991-1993. *Nicotine Tob Res* 2000; 2:263-274
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK: Comorbidity of mental disorders with alcohol and other drugs of abuse. *JAMA* 1990; 264:2511-2518
- Blanco C, Moreyra P, Nunes EV, Saiz-Ruiz J, Ibanez A: Pathological gambling: addiction or compulsion. *Semin Clin Neuropsychiatry* 2001; 6:167-176
- Swadi H: Individual risk factors for adolescent substance use. *Drug Alcohol Depend* 1999; 55:209-224
- Zeitlin H: Psychiatric comorbidity with substance misuse in children and teenagers. *Drug Alcohol Depend* 1999; 55:225-234
- Shaffer HJ: Introduction: youth gambling. *J Gambl Stud* 2000; 16:113-114
- Rogers RD, Robbins TW: Investigating the neurocognitive deficits associated with chronic drug misuse. *Curr Opin Neurobiol* 2001; 11:250-257
- Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC: Psychiatric aspects of impulsivity. *Am J Psychiatry* 2001; 158:1783-1793
- Evenden JL: Varieties of impulsivity. *Psychopharmacology (Berl)* 1999; 146:348-361
- Vitacco MJ, Rogers R: Predictors of adolescent psychopathy: the role of impulsivity, hyperactivity, and sensation seeking. *J Am Acad Psychiatry Law* 2001; 29:374-382
- Dervaux A, Baylé FJ, Laqueille X, Bourdel M-C, Le Borgne M-H, Olié J-P, Krebs M-O: Is substance abuse in schizophrenia related to impulsivity, sensation seeking, or anhedonia? *Am J Psychiatry* 2001; 158:492-494
- Bechara A: Neurobiology of decision-making: risk and reward. *Semin Clin Neuropsychiatry* 2001; 6:205-216

32. Petry NM, Casarella T: Excessive discounting of delayed rewards in substance abusers with gambling problems. *Drug Alcohol Depend* 1999; 56:25–32
33. Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE: Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia* 2001; 39:376–389
34. Arnett J: Reckless behavior in adolescence: a developmental perspective. *Dev Rev* 1992; 12:339–373
35. Spear LP: The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev* 2000; 24:417–463
36. Dorman C, Gaudiano P: Motivation, in *The Handbook of Brain Theory and Neural Networks*. Edited by Arbib MA. Cambridge, Mass, MIT Press, 1998, pp 591–594
37. Kalivas PW, Churchill L, Romanides A: Involvement of the pallidum-thalamocortical circuit in adaptive behavior. *Ann NY Acad Sci* 1999; 877:64–70
38. Rolls ET, Treves A: Motor systems: cerebellum and basal ganglia, in *Neural Networks and Brain Function*. New York, Oxford University Press, 1998, pp 189–226
39. Pennartz CMA, Groenewegen HJ, Lopez da Silva FH: The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioral, electrophysiological and anatomical data. *Prog Neurobiol* 1994; 42:719–761
40. Jentsch JD, Roth RH, Taylor JR: Role for dopamine in the behavioral functions of the prefrontal corticostriatal system: implications for mental disorders and psychotropic drug action. *Prog Brain Res* 2000; 126:433–453
41. Chambers RA, Potenza MN: Impulse control disorders, in *Encyclopedia of the Neurological Sciences*. Edited by Aminoff MJ, Daroff RB. San Diego, Calif, Academic Press (in press)
42. Groenewegen HJ, Wright CI, Beijer AV, Voorn P: Convergence and segregation of ventral striatal inputs and outputs. *Ann NY Acad Sci* 1999; 877:49–63
43. Panksepp J: *Affective Neuroscience*. New York, Oxford University Press, 1998
44. Swanson LW: Cerebral hemisphere regulation of motivated behavior. *Brain Res* 2000; 886:113–164
45. Woodward D, Chang J, Janak P, Azarov A, Anstrom K: Mesolimbic neuronal activity across behavioral states. *Ann NY Acad Sci* 1999; 877:91–112
46. Masterman DL, Cummings JL: Frontal-subcortical circuits: the anatomical basis of executive, social and motivational behaviors. *J Psychopharmacol* 1997; 11:107–114
47. Rolls ET, Treves A: *Neural Networks and Brain Function*. New York, Oxford University Press, 1998
48. Kolomiets BP, Deniau JM, Mailly P, Menetrey A, Thierry AM: Segregation and convergence of information flow through the cortico-subthalamic pathways. *J Neurosci* 2001; 21:5764–5772
49. Chang JY, Janak PH, Woodward DJ: Neuronal and behavioral correlations in the medial prefrontal cortex and nucleus accumbens during cocaine self-administration by rats. *Neuroscience* 2000; 99:433–443
50. Chambers RA, Krystal JK, Self DW: A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry* 2001; 50:71–83
51. O'Donnell P, Greene J, Pabello N, Lewis BL, Grace AA: Modulation of cell firing in the nucleus accumbens. *Ann NY Acad Sci* 1999; 877:157–175
52. Potenza MN: The neurobiology of pathological gambling. *Semin Clin Neuropsychiatry* 2001; 6:217–226
53. Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P: Functional imaging of neuronal responses to expectancy and experiences of monetary gains and losses. *Neuron* 2001; 30:619–639
54. Panksepp J: SEEKING systems and anticipatory states of the nervous system, in *Affective Neuroscience: The Foundations of Human and Animal Emotions*. New York, Oxford University Press, 1998, pp 144–163
55. Kalivas PW: Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. *Brain Res Brain Res Rev* 1993; 18:75–113
56. Strafella AP, Paus T, Barrett J, Dagher A: Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci* 2001; 21:RC157
57. Sano M, Marder K, Dooneief G: Basal ganglia diseases, in *Neuropsychiatry*. Edited by Fogel BS, Schiffer RB, Rao SM. Baltimore, Williams & Wilkins, 1996, pp 805–834
58. Ito R, Dalley JW, Robbins TW, Everitt BJ: Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *J Neurosci* 2002; 22:6247–6253
59. Finch DM: Neurophysiology of converging synaptic inputs from the rat prefrontal cortex, amygdala, midline thalamus, and hippocampal formation onto single neurons of the caudate/putamen and nucleus accumbens. *Hippocampus* 1996; 6:495–512
60. Lavin A, Grace AA: Modulation of dorsal thalamic cell activity by the ventral pallidum: its role in the regulation of thalamocortical activity by the basal ganglia. *Synapse* 1994; 18:104–127
61. Burns LH, Robbins TW, Everitt BJ: Differential effects of excitotoxic lesions of the basolateral amygdala, ventral subiculum and medial prefrontal cortex on responding with conditioned reinforcement and locomotor activity potentiated by intra-accumbens infusions of D-amphetamine. *Behav Brain Res* 1993; 55:167–183
62. Everitt BJ, Wolf ME: Psychomotor stimulant addiction: a neural systems perspective. *J Neurosci* 2002; 22:3312–3320
63. Chambers RA, Self DW: Motivational responses to natural and drug rewards in rats with neonatal ventral hippocampal lesions: an animal model of dual diagnosis schizophrenia. *Neuropsychopharmacology* 2002; 27:889–905
64. Self DW, Nestler EJ: Relapse to drug-seeking: neural and molecular mechanisms. *Drug Alcohol Depend* 1998; 51:49–60
65. Finlay JM, Zigmond MJ: The effects of stress on central dopaminergic neurons: possible clinical implications. *Neurochem Res* 1997; 22:1387–1394
66. Koeppe MJ, Gunn RN, Lawrence AD, Cunningham VJ, Dagher A, Jones T, Brooks DJ, Bench CJ, Grasby PM: Evidence for striatal dopamine release during a video game. *Nature* 1998; 393:266–268
67. Volkow ND, Fowler JS: Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex* 2000; 10:318–325
68. Ljungberg T, Apicella P, Schultz W: Responses of monkey dopamine neurons during learning of behavioral reactions. *J Neurophysiol* 1992; 67:145–163
69. Lipska BK, Jaskiw GE, Chrapusta S, Karoum F, Weinberger DR: Ibotenic acid lesion of the ventral hippocampus differentially affects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat. *Brain Res* 1992; 585:1–6
70. Badiani A, Oates MM, Robinson TE: Modulation of morphine sensitization in the rat by contextual stimuli. *Psychopharmacology (Berl)* 2000; 151:273–282
71. Ferster CB, Skinner BF: *Schedules of Reinforcement*. New York, Appleton-Century-Crofts, 1957
72. Waelti P, Dickinson A, Schultz W: Dopamine responses comply with basic assumptions of formal learning theory. *Nature* 2001; 412:43–48
73. Horger BA, Iyasere CA, Berhow MT, Messer CJ, Nestler EJ, Taylor JR: Enhancement of locomotor activity and conditioned re-

- ward to cocaine by brain-derived neurotrophic factor. *J Neurosci* 1999; 19:4110–4122
74. Gurden H, Tassin JP, Jay TM: Integrity of mesocortical dopaminergic system is necessary for complete expression of in vivo hippocampal-prefrontal cortex long-term potentiation. *Neurosci* 1999; 94:1019–1027
 75. Mulder AB, Arts MPM, Lopes da Silva FH: Short- and long-term plasticity of the hippocampus to nucleus accumbens and prefrontal cortex pathways in the rat, in vivo. *Eur J Neurosci* 1997; 9:1603–1611
 76. Robinson T, Kolb B: Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. *Eur J Neurosci* 1999; 11:1598–1604
 77. Hyman SE, Malenka RC: Addiction and the brain: the neurobiology of compulsion and persistence. *Nat Rev Neurosci* 2001; 2:695–703
 78. Robinson TE, Berridge KC: The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev* 1993; 18:247–291
 79. Deroche V, Le Moal M, Piazza PV: Cocaine self-administration increases the incentive motivational properties of the drug in rats. *Eur J Neurosci* 1999; 11:2731–2736
 80. Brown GL, Linnoila MI: CSF serotonin metabolite (5-HIAA) studies in depression, impulsivity, and violence. *J Clin Psychiatry* 1990; 51(April suppl):31–41
 81. Virkunen M, Rawlins R, Tokola R: CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic violent offenders, fire setters, and healthy volunteers. *Arch Gen Psychiatry* 1994; 51:20–27
 82. Nordin C, Eklundh T: Altered CSF 5-HIAA disposition in pathologic male gamblers. *CNS Spectrums* 1999; 4:25–33
 83. Taylor JR, Jentsch JD: Repeated intermittent administration of psychomotor stimulant drugs alters the acquisition of Pavlovian approach behavior in rats: differential effects of cocaine, d-amphetamine and 3,4-methylenedioxymethamphetamine ("Ecstasy"). *Biol Psychiatry* 2001; 50:137–143
 84. Fuller RW: Fluoxetine effects on serotonin function and aggressive behavior. *Ann NY Acad Sci* 1996; 794:90–97
 85. Cherek DR, Lane SD, Pietras CJ, Steinberg JL: Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. *Psychopharmacology (Berl)* 2002; 159:266–274
 86. White SR, Obradovic T, Imel KM, Wheaton MJ: The effects of methylenedioxymethamphetamine (MDMA, "Ecstasy") on monoaminergic neurotransmission in the central nervous system. *Prog Neurobiol* 1996; 49:455–479
 87. Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR: The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science* 1994; 264:1102–1105
 88. McAllister TW: Neuropsychiatric sequelae of head injuries. *Psychiatr Clin North Am* 1992; 15:395–413
 89. Ames D, Cummings JL, Wirshing WC, Quinn B, Mahler M: Repetitive and compulsive behavior in frontal lobe degenerations. *J Neuropsychiatry Clin Neurosci* 1994; 6:100–113
 90. Raine A, Lencz T, Bihrele S, LaCasse L, Colletti P: Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch Gen Psychiatry* 2000; 57:119–127
 91. Ommaya AK, Salazar AM, Dannenberg AL, Ommaya AK, Chervinsky AB, Schwab K: Outcome after traumatic brain injury in the US military medical system. *J Trauma* 1996; 41:972–975
 92. Barnfield TV, Leatham JM: Incidence and outcomes of traumatic brain injury and substance abuse in a New Zealand prison population. *Brain Inj* 1998; 12:455–466
 93. Delmonico RL, Hanley-Peterson P, Englander J: Group psychotherapy for persons with traumatic brain injury: management of frustration and substance abuse. *J Head Trauma Rehab* 1998; 13:10–22
 94. Dao-Castellana MH, Samson Y, Legault F, Martinot JL, Aubin HJ, Crouzel C, Feldman L, Barrucand D, Rancurel G, Feline A, Syrota A: Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. *Psychol Med* 1998; 28:1039–1048
 95. Liu X, Matochik JA, Cadet JL, London ED: Smaller volume of prefrontal lobe in polysubstance abusers: a magnetic resonance imaging study. *Neuropsychopharmacology* 1998; 18:243–252
 96. Rogers RD, Everitt B, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NB, Hunter J, Carthy T, Booker E, London M, Deakin JFW, Sahakian BJ, Robbins TW: Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology* 1999; 20:322–339
 97. Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, O'Brien CP, Childress AR: Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry* 2002; 51:134–142
 98. McGregor A, Baker G, Roberts DC: Effect of 6-hydroxydopamine lesions of the medial prefrontal cortex on intravenous cocaine self-administration under a progressive ratio schedule of reinforcement. *Pharmacol Biochem Behav* 1996; 53:5–9
 99. Weissenborn R, Robbins TW, Everitt BJ: Effects of medial prefrontal or anterior cingulate cortex lesions on responding for cocaine under fixed-ratio and second-order schedules of reinforcement in rats. *Psychopharmacology (Berl)* 1997; 134:242–257
 100. Karreman M, Westerink BHC, Moghaddam B: Excitatory amino acid receptors in the ventral tegmental area regulate dopamine release in the ventral striatum. *J Neurochem* 1996; 67:601–607
 101. Youngren KD, Daly DA, Moghaddam B: Distinct actions of endogenous excitatory amino acids on the outflow of dopamine in the nucleus accumbens. *J Pharmacol Exp Ther* 1993; 264:289–293
 102. Brady KT, Myrick H, McElroy S: The relationship between substance use disorders, impulse control disorders, and pathological aggression. *Am J Addict* 1998; 7:221–230
 103. Jentsch JD, Taylor JR: Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)* 1999; 146:373–390
 104. Feinberg I: Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res* 1983; 17:319–334
 105. Yates T: Theories of cognitive development, in *Child and Adolescent Psychiatry*. Edited by Lewis M. Baltimore, Williams & Wilkins, 1996, pp 134–155
 106. Moore SM, Rosenthal DA: Venturesomeness, impulsiveness, and risky behavior among older adolescents. *Percept Mot Skills* 1992; 76:98
 107. Siegel J, Shaughnessy MF: There's a first time for everything: understanding adolescence. *Adolescence* 1995; 30:217–221
 108. Leckman JF, Cohen DJ: Tic disorders, in *Child and Adolescent Psychiatry*. Edited by Lewis M. Baltimore, Williams & Wilkins, 1996, pp 622–629
 109. Laviola G, Adriani W, Terranova ML, Gerra G: Psychobiological risk factors for vulnerability to psychostimulants in human adolescents and animal models. *Neurosci Biobehav Rev* 1999; 23:993–1010
 110. Spear LP, Brake SC: Periadolescence: age-dependent behavior and psychopharmacological responsivity in rats. *Dev Psychobiol* 1983; 16:83–109

111. Adriani W, Chiarotti F, Laviola G: Elevated novelty seeking and typical d-amphetamine sensitization in periadolescent compared to adult mice. *Behav Neurosci* 1998; 112:1152–1166
112. Laviola G, Wood RG, Kuhn C, Francis RLP: Cocaine sensitization in periadolescent and adult rats. *J Pharmacol Exp Ther* 1995; 275:345–357
113. Laviola G, Pascucci T, Pieretti S: Striatal dopamine sensitization of D-amphetamine in periadolescent but not adult rats. *Pharmacol Biochem Behav* 2001; 68:115–124
114. Takeuchi Y, Matsushita H, Sakai H, Kawano H, Yoshimoto K, Sawada T: Developmental changes in cerebrospinal fluid concentrations of monoamine-related substances revealed with a Coulochem electrode array system. *J Child Neurol* 2000; 15: 267–270
115. Lambe E, Krimer LS, Goldman-Rakic PS: Differential postnatal development of catecholamine and serotonin inputs to identified neurons in prefrontal cortex of rhesus monkey. *J Neurosci* 2000; 20:8780–8787
116. Garcia-Segura L, Chowen J, Parducz A, Naftolin F: Gonadal hormones as promoters of structural synaptic plasticity: cellular mechanisms. *Prog Neurobiol* 1994; 44:279–307
117. Shughrue PJ, Merchenthaler I: Estrogen is more than just a “sex hormone”: novel sites for estrogen action in the hippocampus. *Front Neuroendocrinol* 2000; 21:95–101
118. Zarrow MX, Naqvi RH, Denenberg VH: Androgen-induced precocious puberty in the female rat and its inhibition by hippocampal lesions. *Endocrinology* 1969; 84:14–19
119. Gorski R: Development of the cerebral cortex, XV: sexual differentiation of the central nervous system. *J Am Acad Child Adolesc Psychiatry* 1999; 38:344–346
120. Sizonenko PC: Endocrinology in preadolescents and adolescents. *Am J Dis Child* 1978; 132:704–712
121. Buchanan CM, Eccles JS, Becker JB: Are adolescents the victims of raging hormones: evidence for activational effects of hormones on moods and behavior in adolescence. *Psychol Bull* 1992; 111:62–107
122. McClelland JL, McNaughton BL, O'Reilly RC: Why are there complementary learning systems in the hippocampus and neocortex? insights from the successes and failures of connectionist models of learning and memory. *Psychol Rev* 1995; 102:419–457
123. Schmajuk NA, Christiansen B, Cox L: Haloperidol reinstates latent inhibition impaired by hippocampal lesions: data and theory. *Behav Neurosci* 2000; 114:659–670
124. Legault M, Wise R: Novelty-evoked elevations of nucleus accumbens dopamine: dependence on impulse flow from the ventral subiculum and glutamatergic neurotransmission in the ventral tegmental area. *Eur J Neurosci* 2001; 13:819–828
125. Woo TU, Pucak ML, Kye CH, Matus CV, Lewis DA: Peripubertal refinement of the intrinsic and associational circuitry in monkey prefrontal cortex. *Neuroscience* 1997; 80:1149–1158
126. Williams BR, Ponesse JS, Schachar RJ, Logan GD, Tannock R: Development of inhibitory control across the life span. *Dev Psychol* 1999; 35:205–213
127. Goodin DS, Squires KC, Henderson BH, Starr A: Age-related variations in evoked potentials to auditory stimuli in normal human subjects. *Electroencephalogr Clin Neurophysiol* 1978; 44:447–458
128. Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL: Quantitative magnetic resonance imaging of human brain development: ages 4–18. *Cereb Cortex* 1996; 6:551–560
129. Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC: Structural maturation of neural pathways in children and adolescents: in vivo study. *Science* 1999; 283:1908–1911
130. Kety SS: Human cerebral blood flow and oxygen consumption as related to aging. *Res Publ Assoc Res Nerv Ment Dis* 1956; 35: 31–45
131. Chugani HR, Phelps ME, Mazziotta JC: Positron emission tomography study of human brain functional development. *Ann Neurol* 1987; 322:487–497
132. Yakovlev PI, Lecours AR: The Myelogenetic Cycles of Regional Maturation of the Brain. Philadelphia, FA Davis, 1967
133. Nudo RJ, Masterton RB: Stimulation-induced [¹⁴C]2-deoxyglucose labeling of synaptic activity in the central auditory system. *J Comp Neurol* 1986; 245:553–565
134. Lewis DA: Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology* 1997; 16:385–398
135. Huttenlocher PR: Synaptic density in human frontal cortex: developmental changes and effects of aging. *Brain Res* 1979; 163:195–205
136. Anderson SA, Classey JD, Conde F, Lund JS, Lewis DA: Synchronous development of pyramidal neuron dendritic spines and parvalbumin-immunoreactive chandelier neuron axon terminals in layer III of monkey prefrontal cortex. *Neurosci* 1995; 67: 7–22
137. Rutherford LC, Nelson SB, Turrigiano GG: BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. *Neuron* 1998; 21:521–530
138. Miller KD: Synaptic economics: competition and cooperation in synaptic plasticity. *Neuron* 1996; 17:371–374
139. Alexander GE: Functional development of frontal association cortex in monkeys: behavioral and electrophysiological studies. *Neurosci Res Prog Bull* 1982; 20:471–479
140. Spitzer M: The Mind Within the Net. Cambridge, Mass, MIT Press, 1999
141. Milberger S, Biederman J, Faraone SV, Wilens T, Chu MP: Associations between ADHD and psychoactive substance use disorders. *Am J Addict* 1997; 6:318–329
142. Biederman J, Wilens T, Mick E, Spencer T, Faraone SV: Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. *Pediatrics* 1999; 104:1–5
143. Lynskey MT, Hall W: Attention deficit hyperactivity disorder and substance use disorders: is there a causal link? *Addiction* 2001; 96:815–822
144. DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM: Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. *Bipolar Disord* 2001; 3:53–57