Published in final edited form as:
Am J Psychiatry. 2003 June ; 160(6): 1041–1052.

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

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Abstract

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.

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—

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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 strategies 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 pallidus) 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 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 raphae nuclei to motivational circuitry, including the ventral 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-hydroxyindole-acetic 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 twofold 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 developmental 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.

Acknowledgments

Supported by a Veterans Administration Special Neuroscience Research Fellowship Grant and grants from the National Alliance for Research on Schizophrenia and Depression (Young Investigator Award), the National Institute on Drug Abuse (DA-11717, DA-00167), the American Psychiatric Association (DA-00366), and the National Center for Responsible Gaming.

The authors thank George Heninger for comments on the manuscript.

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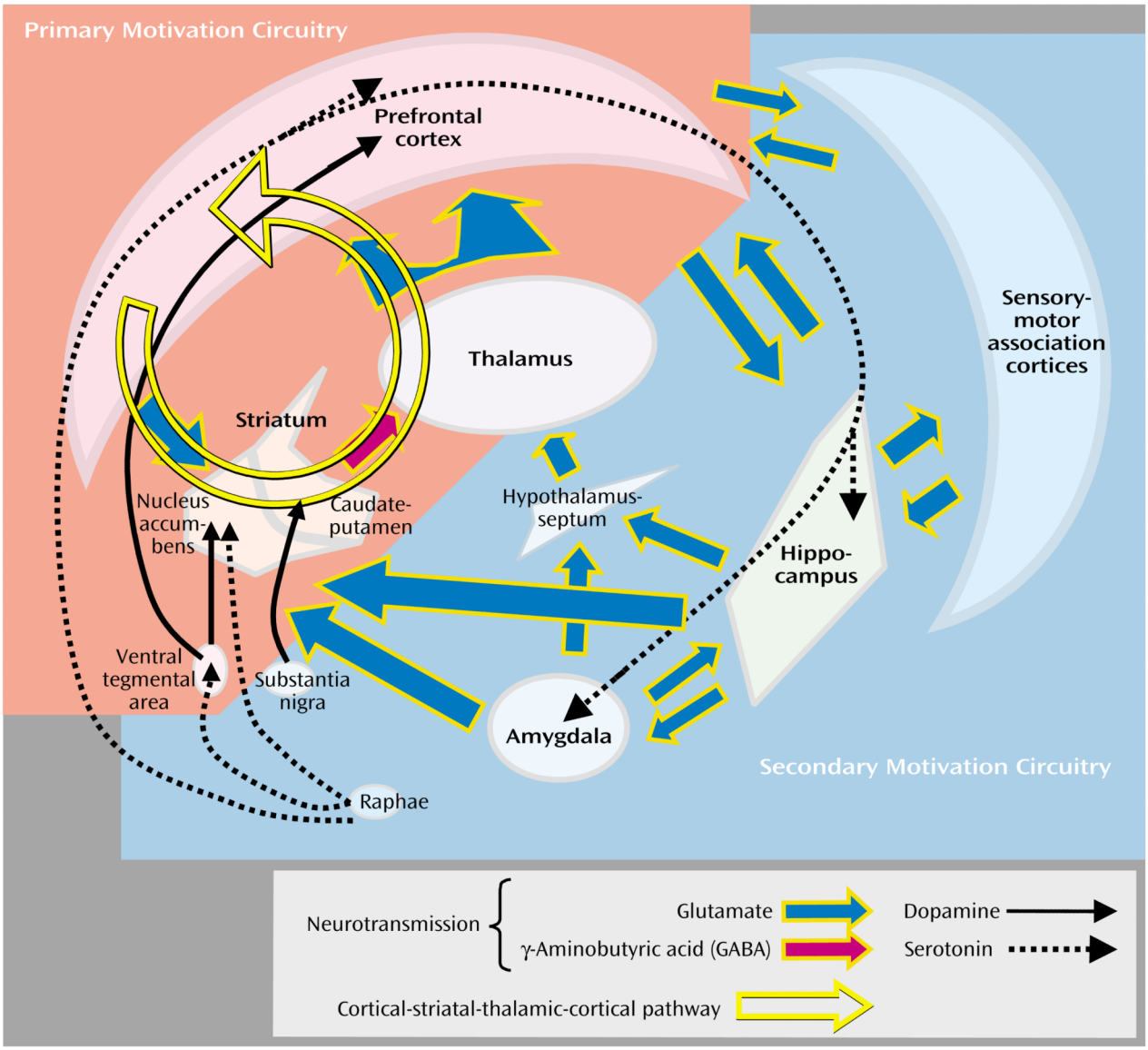

FIGURE 1. Major Motivational Brain Circuitry Putatively Involved in Impulsivity, Decision Making, and Drug Addiction[a]

[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.

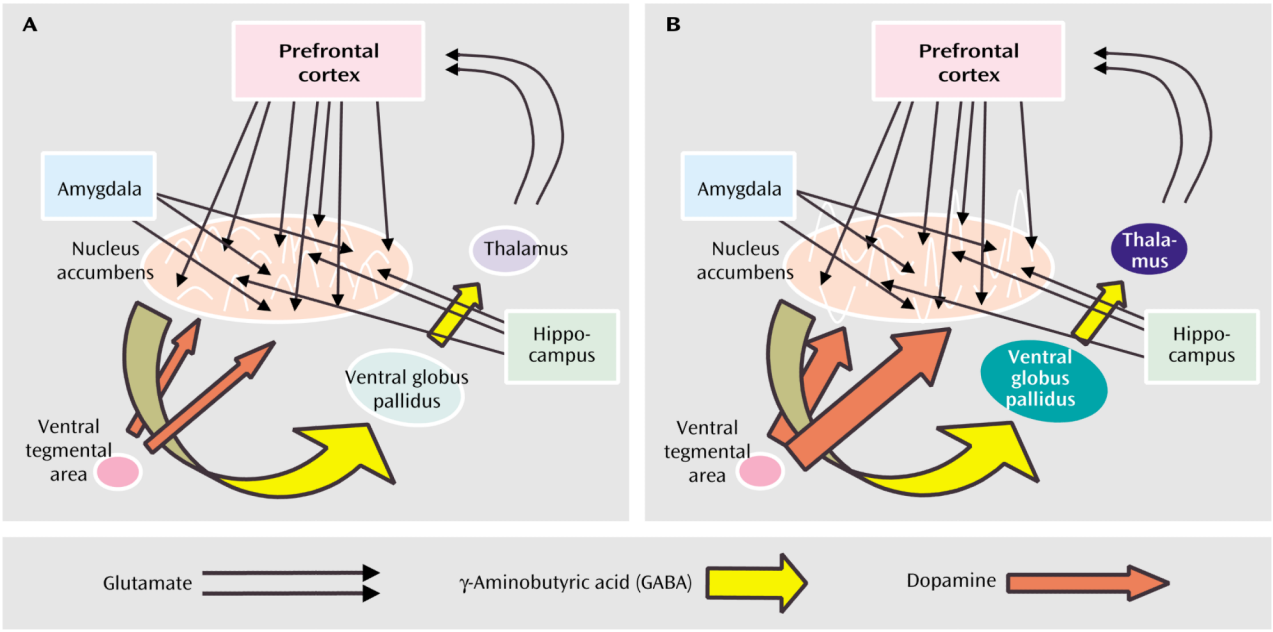

FIGURE 2. Cortical-Striatal-Thalamic-Cortical Loops Within Primary Motivation Circuitry Involved in the Representation of Motivated Drives and the Neurocomputational Events of Motivational Decision Making and Behavioral Instigation[a]

[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.