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Neurodevelopment, Impulsivity, and Adolescent Gambling

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The prevalence of problem and pathological gambling in adolescence and young adulthood has been found to be two- to fourfold higher than in adulthood. Given that these high rates might predict future increases across all age groups, it is important to explore the causes of the elevated rates of problem and pathological gambling among youths. This article reviews evidence for a neurobiological basis for adolescent vulnerability to problem and pathological gambling behaviors. We propose that a common trait motif of impulsivity might underlie phenomenology of pathological gambling, commonly comorbid psychiatric disorders, and related aspects of adolescent behavior. Recent advances in understanding the brain mechanisms involved in motivation, reward, and decision-making allow a discussion of neural circuitry underlying impulsivity. Emerging data indicate that important neurodevelopmental events during adolescence occur in brain regions associated with motivation and impulsive behavior. We hypothesize that immaturity of frontal cortical and subcortical monoaminergic systems during normal neurodevelopment underlies adolescent impulsivity as a transitional trait-behavior. While these neurodevelopmental processes may confer advantage by promoting a learning drive for optimal adaptation to adult roles, they may also confer an increased vulnerability to addictive behaviors such as problem and pathological gambling. An exploration of the developmental changes in neural circuitry involved in impulse control has significant implications for understanding adolescent behaviors and treating problem and pathological gambling among youths.

KEY WORDS: neural networks; neurodevelopment; serotonin; dopamine; prefrontal cortex.

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INTRODUCTION

Epidemiological aspects of psychiatric disorders can provide important information regarding their neurobiological as well as their socio-cultural causes. Investigations have consistently revealed high rates of gambling, problem gambling and pathological gambling (PG) in adolescents as compared with adults (Derevensky and Gupta 2000; Gupta and Derevensky 2000; Shaffer 2000; Shaffer and Hall 2001; Shaffer et al. 1999). The proliferation of national gambling venues has been suggested as an important socio-cultural risk factor leading to increases in the incidence of PG (Eisen et al. 2001). This article focuses on how the high rates of gambling, problem gambling and PG in adolescent and young adult populations may result in part from neurobiological processes involved in normal neurodevelopment during these epochs. We examine the plausibility of a link between adolescent neurodevelopment and gambling behaviors by exploring: 1) impulsivity as a trait-behavior common in adolescence and psychiatric conditions often comorbid with PG; 2) neural circuits implicated in impulse control; and, 3) changes in these neural networks during adolescence. Examination of impulsivity and PG in the context of adolescent neurodevelopment has the potential both to increase our general understanding of the biological bases of these processes and to provide a rational basis for the development of treatments for problem gambling and PG in young populations.

GAMBLING IN ADOLESCENCE

Simultaneous with the proliferation of legalized gambling in the U.S. and elsewhere over the last 20 years, reports have identified high and apparently rising prevalence rates of gambling behaviors (including problem gambling and PG) among adolescents (Diclemente et al. 2000; Shaffer and Hall 2001). In a study of five surveys conducted between 1984 and 1988, the median fraction of middle and high school students gambling in the last 12 months was 45%, while the median from nine surveys conducted between 1989 and 1999 was 66% (Jacobs 2000). The median fraction of children with "serious gambling-related problems," described as at-risk, problem or potential problem gamblers, was 10% in the 1984–88 period and 14% during 1989–99

(Jacobs 2000). Adult populations have concurrently demonstrated a rise in rates of problem gambling and PG (Shaffer et al. 1999). Although prevalence estimates of PG in adults have generally ranged from approximately 1% to 2% (Cunningham-Williams and Cottler 2001; Gerstein et al. 1999; James 1999; Shaffer et al. 1999; Spunt et al. 1998), a meta-analysis of prevalence estimate studies performed in North America found significantly higher rates of problem gambling and PG in adults in studies performed from 1994–1997 as compared with those performed in 1993 or earlier (Shaffer et al. 1999). Together, existing data support the notion that the prevalence of PG is higher in adolescents and young adults compared to middle and older adult subgroups, and that prevalence rates in general appear to be rising (Cunningham-Williams and Cottler 2001). Children who gamble typically start around age 12, and participate in a wide array of different forms of gambling like their adult counterparts, including state-supported lotteries (Jacobs 2000). Although further study of youth gambling is warranted to examine a possible role for method-related over-estimations of the severity and/or prevalence of problem and pathological gambling among adolescents, existing data suggest that there is a heightened vulnerability to problem gambling and PG during adolescence. The data also raise concerns regarding the possibility of a significant future increase in adult PG, particularly since earlier age of onset of gambling has been found to be associated with more severe gambling-related problems later in life (Winters et al. 1990).

IMPULSIVITY AS A COMMON DENOMINATOR IN PATHOLOGICAL GAMBLING, ASSOCIATED PSYCHIATRIC CONDITIONS, AND ADOLESCENCE

The higher rates of problem gambling in youths as compared with adults mirrors the pattern of substance abuse in adolescents vs. adults (Shaffer 2000). The increased occurrence of substance use disorders (primarily involving nicotine and alcohol) in both adolescents who gamble and adult pathological gamblers suggests an etiological relationship between substance abuse and gambling disorders (Blanco et al. 2001; Potenza 2001; Potenza and Wilber 2001; Winters and Anderson 2000). In addition to substance use disorders, other psychiatric disorders have increased prevalence in the setting of PG, including

affective disorders, schizophrenia and antisocial personality disorder (Chambers and Potenza 2001; Cunningham-Williams and Cottler 2001; Cunningham-Williams et al. 1998). It is notable that these psychiatric conditions are also, along with PG, associated with an increased risk for a substance use disorder (Reigier et al. 1990). These data, along with observations that pathological gambling involves strong motivations to engage in gambling, and subjective feelings of reward, withdrawal, and craving for gambling, support the categorization of PG as "a non-pharmacologic addiction" (Blanco et al. 2001; Holden 2001). This view is corroborated by neuroimaging findings that gambling-associated cognitive and motivational events, or responses of pathological gamblers to gambling-related stimuli, are associated with metabolic changes in brain regions implicated in studies of substance use disorders (Breiter et al. 2001; Breiter et al. 1997; Holden 2001; Potenza and Wilber 2001). In addition, studies of male twins indicate shared genetic contributions for the development of PG and alcohol dependence (Slutske et al. 2000). Consistent with this notion, clinical-epidemiologic features of age or gender-related subgroups with alcoholism (e.g., Cloninger's Type I/II distinctions and gender-related differences in onset and illness course) have been suggested to apply to individuals with PG, further suggesting a link between PG, substance use disorders and impulsivity (Lesieur 2000; Potenza 2001; Potenza et al. 2000; Taveres et al. 2001). Together, these findings support the DSM-IV-TR classification of PG as an impulse control disorder, which along with substance use disorders, can be considered within a broader family of diagnoses characterized by impaired impulse control (DSM-IV-TR 2000; Potenza and Hollander 2002).

Impulsivity is a motif observed throughout a diversity of neuropsychiatric disorders marked by disturbances in reward motivation (Zuckerman 1993). Regardless of the psychiatric diagnosis, implulsivity is often identified as a feature associated with attainment of particular rewards such as addictive drugs, sex, food, or social power (via violence) (Evenden 1999). If the particular form of reward-directed activity becomes repetitive, patterned and/or enacted upon the exclusion of other normal motivations, the impulsive behavior can be considered as having transitioned into a 'compulsive' behavior. Persons with psychiatric disorders can show impulsivity operating in multiple behavioral domains, in regard to different forms of reward attainment, sometimes pervading nearly the entire behavioral repertoire of the individual. Pervasive impulsivity is commonly observed in five representative clinical contexts: 1) personality disorders; 2) affective disorders; 3) schizophrenia spectrum disorders; 4) substance intoxication and/or dependence; and 5) central neurological diseases (Chambers and Potenza in press; Evenden 1999). It is notable that these clinical contexts overlap very closely with the set of psychiatric conditions that are commonly identified with PG. Since impulsive reward attainment can lead to compulsive reward seeking, diagnostic groups with pervasive impulsivity may have a general vulnerability to advance to one or more of a variety of forms of compulsive or addictive-like behaviors, including PG or drug addiction (Brady et al. 1998; Patterson and Newman 1993). Thus, impulsivity appears to be a common behavior identified in PG as well as the conditions most often comorbid with it, suggesting its candidacy as an important trait-marker of the primary brain mechanisms responsible for the particular epidemiological linkage of these disorders. Since adolescence is regarded as a developmental phase in which impulsive behavior is normally more frequent (Clayton 1992), impusivity may be an important common denominator linking increased gambling, problem gambling and PG with adolescence.

IMPULSIVITY, ACTION-DECISION MAKING, AND PATHOLOGICAL GAMBLING

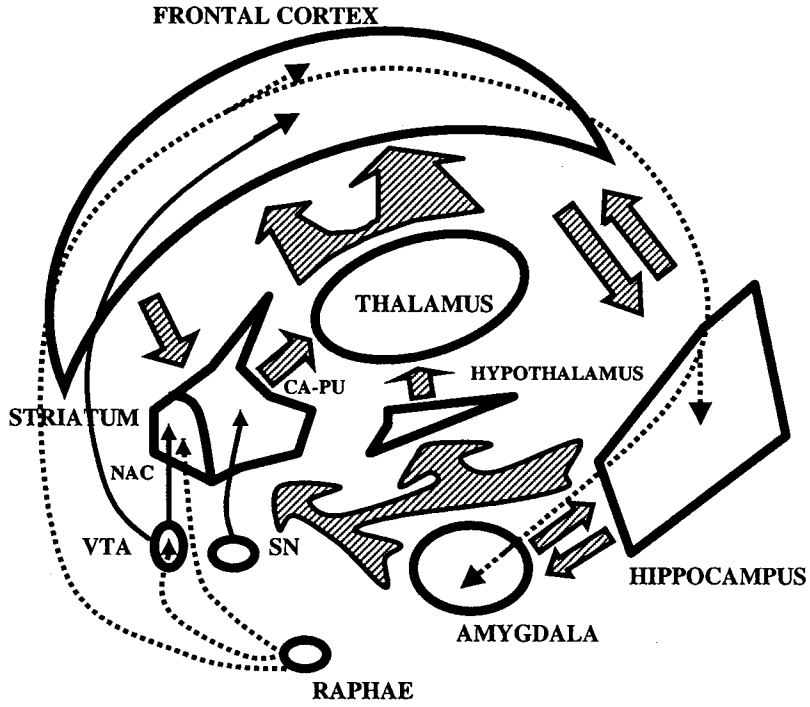
Given data supporting an important empirical connection between impulsivity and PG, it is important to explore conceptual/operational data regarding this link. Examination of these linkages will facilitate a discussion of the neurobiological substrates involved in PG as an extension of our understanding of the neurobiological substrates involved in impulsivity.

Common among the diversity of forms of gambling is participation in ritualized risk-taking in which a decision is made in an attempt to achieve benefit in the face of ambiguous information concerning the relative likelihood and/or values of potentially negative or beneficial outcomes. Virtually all behaviors (e.g., driving one's car to work) involve risk-taking, but the actions performed during the course of one's daily routine usually entail clear benefit and low chance of negative results. By comparison, in gambling, the possible outcomes often represent one of two relatively polarized extremes of a cost-benefit

spectrum, and the distinction in the probabilities of either outcome, relative to each other and their cost-benefits, is generally not as pronounced. In gambling, the bet defines the negative outcome, or cost, that might be incurred from the decision to gamble, placed in hopes of gaining something of greater value. Resource investment, similar to betting, often occurs in routine decision-making. Investing in the stock market can be classified as gambling, although some might argue that more risky investing patterns (e.g., day trading, buying and selling derivatives) seem more similar to traditional forms of gambling (e.g., casino gambling) than less risky patterns (e.g., buying and selling of mutual funds). Thus, gambling may be viewed as a special case of the action-decision function that humans constantly perform while producing their complete motivational/behavioral repertoire. PG may then be viewed as a powerful attraction and tendency to engage in forms of ritualized risk-decision making at the expense of participation in or benefits incurred from the usual low risk action-decisions that allow daily functioning. This formulation suggests an approach toward understanding the neuroanatomy involved in PG by understanding the fundamental brain systems involved in action-oriented decision-making (Bechara 2001; Potenza and Wilber 2001).

Action-oriented decision-making may be conceptualized as a three-component process involving: (1) input: the accumulation and packaging of sensory input into a general contextual frame; (2) processing: the representation, evaluation and choosing of behavioral response options to this contextual frame; and (3) output: the planning and implementation of a motor output or behavioral response that is the outward realization of the action-oriented decision (Chambers and Potenza in press). Accumulated data allow for the proposal of the mapping of these functions onto specific regions of brain circuitry (Figure 1): (1) input: sensory cortices, subcortical autonomic brain centers, amygdala, hypothalamus, hippocampus (Bechara et al. 2000; Davidson et al. 2000; Robertson 1996); 2) processing: prefrontal (including orbitofrontal, dorsolateral prefrontal, and ventromedial prefrontal cortices), ventral striatum, thalamus, and (monoaminergic) brainstem nuclei (Anderson et al. 1999; Bechara 2001; Davidson et al. 2000); 3) output: premotor-motor cortex, dorsal striatum, thalamus, hypothalamus, cerebellum and brainstem nuclei (Sano et al. 1996). Several additional brain regions implicated in motivation (e.g., anterior cingulate cortex) and decision making (e.g., insula cortex) which are ana-

Figure 1
Major Neuroanatomical Circuitry Involved in Motivation and Action-Oriented Decision-Making



Note: Sensory cortices, amygdala, hippocampus, hypothalamus, and subcortical autonomic brain centers contribute to highly integrated, multimodal representations in the frontal cortex and striatum of the contextual frame that informs action-oriented decision-making. Frontal/prefrontal cortex (including orbitofrontal, dorsolateral prefrontal, and ventromedial prefrontal cortices), ventral striatum (nucleus accumbens (NAc)), thalamus, and brainstem nuclei (dopaminergic afferents from the ventral tegmental area (VTA); serotonergic afferents from the dorsal raphae) mediate the representation, evaluation, and choosing of behavioral response options to this contextual frame. Premotor-motor cortex, dorsal striatum (caudate-putamen (CA-PU)), thalamus, brainstem nuclei (dopaminergic afferents from the substantia nigra (SN)), hypothalamus and cerebellum (not shown) implement and control motor output programs or behavioral responses in execution of the action-decision. Major excitatory glutamatergic projections and important inhibitory GABAergic projections from striatum to thalamus: wide stippled arrows. Dopaminergic afferents: thin dark arrows. Serotonergic afferents: thin stippled arrows.

tomically connected to the prefrontal cortex, and other listed brain regions have been omitted from the figure for the sake of clarity, although it is recognized that activity in these brain regions appears important in mediating aspects of impulse control and motivated behaviors (Bechara 2001; Grant et al. 2000; Wexler et al. 2001).

In the following sections, we will focus on the second or 'processing' component of action-decision making and propose a corresponding neuroanatomy termed primary motivation circuitry (PMC; Figure 1). In conceptualizing the function of the PMC, it is important to recognize that the proper functioning of this subsystem requires concurrent activity and integration of multiple global neural circuits that embody the 'input' and 'output' processes described above. These are proposed to be encompassed within a secondary motivation circuitry (SMC) representing sensory, motor, internal homeostatic, affective and memory information. The outcome of the demanding and complex process of action-oriented decision-making is thus vulnerable to poor coordination or disordered functioning of any of the involved sub-systems, resulting in what might be assessed as an inappropriate action outcome. Within this construct, behaviors (and the decisions they reflect) are enacted with 'impulsivity' or, in some circumstances, 'in poor judgment,' contingent on the form, timing, or pairing of the behavioral response with respect to the environmental context. In terms of the functioning of the PMC, impulsivity leading to disadvantageous action-oriented decision-making may be viewed as a response selection from among a pool of neural representations of possible behavioral options defined by: 1) the representation and instigation of an 'abnormal' motivated drive; 2) an abnormally low threshold for the enactment of a certain motivated drive; or, 3) the mis-prioritization of a motivated drive. Any of these scenarios could result from a relative inability of the brain to assess or represent appropriately the possible beneficial or detrimental effects of behavioral actions relevant to the environmental context, or to associate them accurately with the pool of possible behavioral options represented in motivational circuitry. These scenarios can be encapsulated into one conceptualization of impulsivity as related to disadvantageous action-oriented decision-making as an apparent abnormality in risk-benefit assessment associated with behavioral actions.

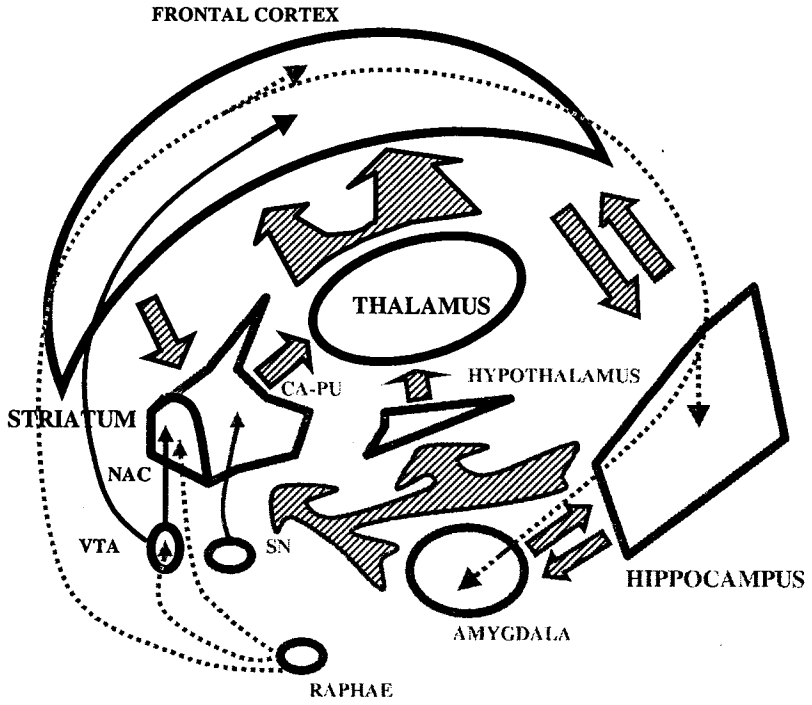
Data exists to support the notion that individuals with impaired impulse control exhibit abnormalities in risk-benefit decision making

in both gambling and non-gambling activities, and that their cognitive or emotional sense of what distinguishes gambling from other decisions of daily living may be compromised. Individuals with alcoholism, drug dependence, antisocial personality disorder or pathological gambling have been shown to discount delayed rewards at an excess rate, and such patterns have been thought to represent a functional measure of impulsivity in these groups (Bauer 2001; Bickel et al. 1999; Crean et al. 2000; Madden et al. 1997; Petry 2001a; Petry 2001b; Petry and Casarella 1999). Individuals with substance use disorders and/or pathological gambling have also been shown to perform disadvantageously on gambling tasks used to assess decision making performance (Bechara 2001; Bechara et al. 1994; Cavedini et al. 2001; Grant et al. 2000; London et al. 2000; Petry 2001c; Potenza 2001; Rogers et al. 1999; Rogers and Robbins 2001). Deficits in emotional or cognitive processes that contribute to neural representations of the possible negative consequences of gambling may impair the capacity to learn from past losses, or assess risks associated with action-oriented decision-making (Bechara 2001; Bechara et al. 2000). These deficits could produce an inability to inhibit motivated drives to gamble, leading to persistent gambling. A person may also be attracted to specific features of gambling that distinguish it from usual, non-gambling decisions of daily living. A heightened subjective benefit or mental gratification associated with the excitement of participating in a relatively unpredictable risk-decision process may thus also contribute to persistent gambling. This last scenario represents an increase in the promotion of a motivated drive to gamble. Thus, individuals with impaired impulse control may show persistence in gambling or other addictive behaviors for a variety of types of reasons, including abnormalities in inhibitory control, decision-making or motivational proponent processes, or some combination thereof.

NEUROBIOLOGICAL SUBSTRATES OF IMPULSIVITY

Neurobiological studies of impulsivity link an apparent disturbance in risk-benefit decision making with events in neural motivation systems. Basic and clinical evidence suggests that neural processing of risk-benefit decision making involves representations of both promotional and inhibitory information within a distributed neural network

Figure 2
A Primary Motivation Circuit (PMC), Shown in Bold, Subserves a 'Central Processing' Component of Action-Oriented Decision-Making

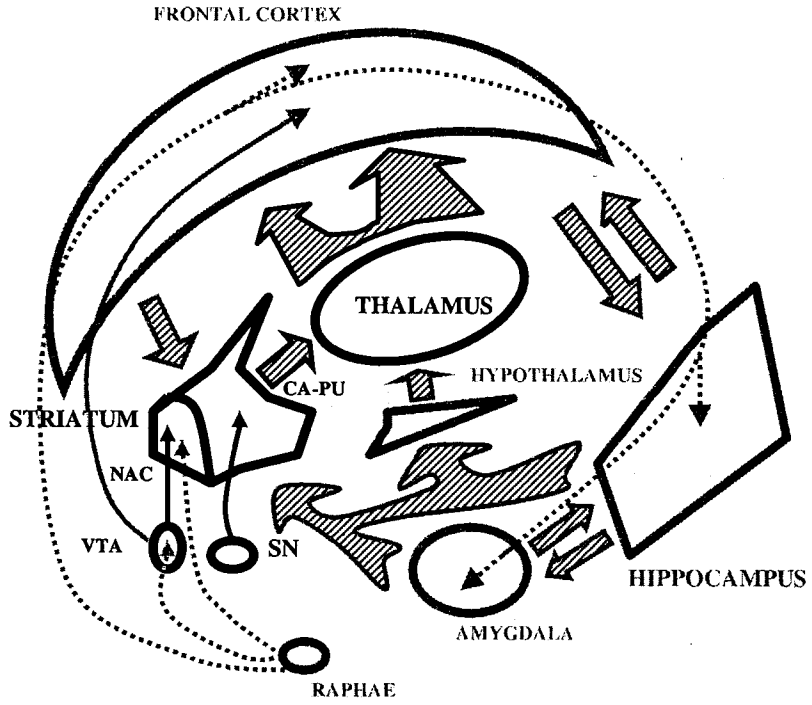


Note: Within this system, behavioral outcomes are determined contingent on the evaluation and processing of information representing the promotion and inhibition of motivated drives. Glutamatergic input from the frontal cortex and limbic regions and dopamine discharge from the VTA influences firing patterns in ensembles of NAc neurons, computationally resolving inhibitory and promotional motivational representations underlying the choosing and instigation of motivated drives into behavioral action. Secondary motivation circuitry (SMC), shown in light gray, provides sensory, affective, autonomic, and memory information via afferents from the amygdala, hippocampus, brainstem nuclei (serotonin sources), and hypothalamic sources to the PMC. The dorsal striatal (CA-PU and SN) portion of the SMC along with motor cortices and hypothalamic regions provides motor output capacity to the PMC.

that we define here as PMC (Chambers and Potenza in press; Potenza 2001). This network is organized as parallel loops of serial neuronal projections from the prefrontal cortex (PfC), to ventral striatum (nucleus accumbens (NAc)), to thalamus, and back to the cortex (Masterman and Cummings 1997; Ongur and Price 2000) (Figure 2). Neurotransmission occurs between nodes in this loop composed of dense collections of neuronal bodies within the cortex and subcortical nuclei (Kolomiets et al. 2001). Intranodal transmission utilizes excitatory glutamatergic transmission in and out of the cortex, and inhibitory GABAergic (gamma-aminobutyric acid receptor) neurotransmission between subcortical regions of the circuit (Lavin and Grace 1994; Masterman and Cummings 1997). GABAergic transmission also occurs locally within nodes, gating the flow of excitatory activity between anatomical nodes of the loop (Yang and Mogensen 1985). These GABAergic interneurons are also thought to help neural networks encode a vast number of representations, and they facilitate dynamic competition between excitatory inputs contributing to mechanisms of neuroplasticity and learning (Granger et al. 1996; Intrator 1998; O'Donnell et al. 1999; Rutherford et al. 1998). Activity is further modulated in the prefrontal cortex and NAc by fibers utilizing dopamine (DA) and serotonin (5-HT), originating in the midbrain's ventral tegmental area (VTA) and raphae nuclei, respectively (Ravel et al. 2001).

The SMC, including afferent input from the amygdala, hippocampus, brainstem (dorsal raphe) and hypothalamus (Figure 2), provides the PMC with contextual memory, affective, motor, autonomic and hormonal information that informs the decision-making process (Bechara et al. 2000; Panksepp 1998c; Pennartz et al. 1994). Hypothalamic nuclei influence PMC function by providing 'instinctual' motivational programming relevant to survival such as nutrient ingestion, social and sexual behavior (Swanson 2000). Communication within motivational circuits also occurs via a wide variety of neurotransmitters including norepinephrine, endogenous opiates and other neuropeptides, and neurohormones, such as testosterone. Although many of these neurochemicals have been implicated in impulsive behaviors and PG (Buchanan et al. 1992; Leary and Dickerson 1985; Potenza 2001; Roy et al. 1989; Shinohara et al. 1999), arguably the most well-studied and consistently implicated systems are those involving dopamine (DA) and serotonin (5-HT), as described in greater detail below.

Figure 3
Promotional Motivation Substrates, Shown in Bold, Facilitate the Action of a Motivated Drive in Association with a Reward-Benefit



Note: Data are consistent with a role for dopamine discharge into the striatum operating: 1) in the short-term like a 'go signal' to translate a motivated drive into behavioral action; and, 2) in the long-term to influence neuroplastic processes underlying motivational memory and repertoire.

Promotional Motivating Substrates

Promotion of motivated drives occurs in a neural network that holds representations of possible motivational drive options and instigates their enactment (Figure 3). Multiple lines of evidence suggest that important activity pertaining to this function of PMC is localized to the NAc (Cardinal et al. 2001). Here, afferent excitatory glutamatergic projections from the frontal cortex, amygdala, and hippocampus, convey motor planning, sensory, affective, and contextual

memory information by influencing firing patterns among individual neurons that comprise NAc neuronal ensembles (Finch 1996; O'Donnell et al. 1999; O'Donnell and Grace 1995). A broad repertoire of motivational states and/or possible motivational drive options could then be represented by a corresponding diversity of firing patterns within these NAc ensembles (Pennartz et al. 1994). VTA afferents provide DA modulation of neuronal ensembles within the NAc, which also effects how they respond to the glutamatergic inputs described above (O'Donnell et al. 1999). DA release into the NAc is provoked by excitatory signals from cortex and other areas (Kalivas 1993; Strafella et al. 2001), operating as part of a "foraging/exploration/investigation/curiosity/interest/expectancy/seeking system" in the brain, where DA release works like a 'go' signal (Panksepp 1998b). DA release into the ventral striatum (and specifically the NAc) parallels the role of DA transmission originating from the substantia nigra (a dorsal analogue of the VTA) into dorsal striatum (caudate-putamen), a system involved in the initiation and control of concrete motor activity and the pathophysiology of Parkinson's disease (Sano et al. 1996). However, ventral striatal DA transmission from the VTA into the NAc is involved in more preliminary stages of motor planing than the dorsal system, such as the representation and control of thoughts and motivational processing (Chambers et al. 2001). The list of stimuli and/or activities that correspond to DA release into the NAc is extensive and includes exposure to addictive drugs (nicotine, cocaine, opiates, cannabis, amphetamine, alcohol), natural rewards (food, sex, or other resources), rewarding situations (video game playing), stimuli associated with addictive drugs or natural rewards, and stressful or strongly aversive stimuli (Finlay and Zigmond 1997; Koepp et al. 1998; Panksepp 1998b; Self and Nestler 1998; Volkow and Fowler 2000). The drive to seek and explore the unknown is a primary motivation that can confer an evolutionary advantage to animals and environmental novelty also provokes mesolimbic DA release (Ljungberg et al. 1992). That which is novel is also unpredicted and rewards delivered in an intermittent, unpredictable fashion have a greater capacity both to cause DA release as well as maintain reward-conditioned behavior over many repeated trials (Ferster and Skinner 1957; Waelti et al. 2001). This aspect of mesolimbic DA reward mechanisms may explain, in part, the particular excitement associated with the seemingly unpredictable outcomes in gambling, associated with sustained participation in gambling.

A growing body of literature also suggests that DA release in the NAc can also impact on reward or conditioned learning by influencing neuroplastic processes. Repeated DA release in the NAc, provoked by addictive drugs has been shown to induce changes in cellular proteins involved in intracellular receptor signaling pathways, gene expression, and cellular architecture (Nestler and Aghajanian 1997; Nestler 2001). Further, DA transmission in both the NAc and prefrontal cortical regions that project back to the NAc have been implicated in interneuronal mechanisms of learning and plascticity including long-term potentiation (LTP) (Gurden et al. 1999; Mulder et al. 1997). These neuronal processes are thought to underlie behavioral sensitization whereby the motivational drive associated with a reward becomes increasingly stronger as that reward context is repeatedly experienced (Robinson and Berridge 1993). Sensitization, as an increase in salience or desirability of a particular contextual reward, produces reward acquisition behavior that becomes increasingly impulsive and later compulsive in nature (Jentsch and Taylor 1999; Robinson and Berridge 1993). Impulsivity in the setting of drug addiction or sexual addictions, eating disorders, or PG may reflect a general predisposition to having an accelerated sensitization of DA-related reward circuitry. Additional studies are required to test this hypothesis and determine the extent to which it might apply to groups or sub-groups of individuals with addictive disorders.

Inhibitory Motivation Substrates

Arguably the most widely-implicated neurotransmitter system with regard to impaired impulse control is 5-HT. 5-HT projections originate from the raphae nuclei in the midbrain and transmit diffusely throughout the brain. Central markers of 5-HT activity have been found to be decreased in persons in the context of impulsive acts of violence, suicide, fire-starting, and pathological gambling (Brown and Linnoila 1990; Nordin and Eklundh 1999; Virkunnen et al. 1994). In rats, pharmacological injury to 5-HT systems results in increased reward or DA-related impulsivity (Taylor and Jentsch 2001). Treatment with pro-serotonergic antidepressant medications have also been associated with decreases in social aggression in rats corresponding to clinical reports of decreased impulsivity and risk of violence in patients (Fuller 1996). Although the mechanism for these findings has not been precisely established, serotonergic projections to motivation circuits including VTA, NAc, PfC, amygdala, and hippocampus are likely involved (Kalivas 1993; White et al. 1996).

Multiple lines of evidence link impulsivity with compromise in PfC function. For example, Phineas Gage, after suffering a severe frontal lobe injury in 1848, demonstrated pervasive motivational impulsivity associated with affective instability, personality changes, poor decision-making and executive planning, and apparent indifference to social contextual cues (Damasio et al. 1994). These deficits, currently thought to be the result of damage to his ventromedial cortex bilaterally, were observed in the relative absence of intellectual deficits as determined by traditional measures. Phineas Gage's pattern of symptomatology is consistent with anatomical data highlighting the distributed axonal interconnectedness of PfC regions with the ventral striatum, amygdala and hippocampal formation and suggests a central role for the PfC in information processing in both PMC and SMC (Carr and Sesack 1996; Groenewegen et al. 1997). As a center of multi-modal information evaluation and processing, the PfC functions in cooperation with the hippocampus, like a working-memory work bench which can hold data on line until a decision is made (Goldman-Rakic 1987; Heckers et al. 1998; McClelland et al. 1995). In this manner, the PfC functions as a central evaluator, executor or inhibitor of motivational drives and, to some extent, affective states and memory traces, which themselves influence motivational drives. Excitatory glutamatergic projections from the PfC to the NAc and the VTA influence neuronal firing in these regions, DA release into the NAc, and neuroplastic processes in the NAc (Karreman et al. 1996; Pennartz et al. 1993; Youngren et al. 1993). Compromise of PfC or its inputs to the NAc could: 1) limit the variety of representations of motivational drive options in the NAc; 2) lower the threshold by which NAc neuronal ensembles respond to the "go signal" provided by DA influx; and/or, 3) limit the overall capacity of the NAc to undergo neuroplastic changes that would normally decrease the strength of motivated drives deemed "inappropriate" by prior experience. Any of these possibilities, arising from poor frontal functioning, regardless of the specific pathological process involved, could result in the increased probability of performing "inappropriate" motivated drives, viewed clinically as impulsivity leading to disadvantageous behaviors. This notion is generally consistent with empirical observations that a variety of neuropsychiatric condi-

tions involving abnormal PfC functioning, including antisocial personality, mood disorders, schizophrenia, substance intoxication and dependence, dementias, traumatic brain injury, and other neurological disorders, are often associated with disinhibited, impulsive, compulsive or stereotyped behavior (Ames et al. 1994; McAllister 1992; Raine et al. 2000). In terms of PG, impulsive individuals with PfC compromise may not be as sensitive to or aware of negative consequences via "gut feelings" that are neurally represented in PfC and associated emotional or memory systems (Bechara 2001; Bechara et al. 1999). As such, abnormalities in PfC function may be related to multiple types of impaired impulse control; e.g., decreased inhibition and disadvantageous decision-making.

DEVELOPMENTAL NEUROBIOLOGICAL CHANGES IN ADOLESCENCE: MATURATION OF NEURAL SUBSTRATES INVOLVED IN IMPULSE CONTROL

Adolescence is a phase of profound neurodevelopmental change as well a period of robust physical development. During this time, the young person acquires increasingly adult-like cognitive, motivational and emotional styles that are distinct from those observed in childhood (Feinberg 1983; Yates 1996). Adolescents frequently seek adult experiences and often delight in their initial participation in these events (Moore and Rosenthal 1992). The accumulation of new conceptual and emotional tools that accompany maturation into an adult brain may be correlated with heightened interest and attraction to current culture, music, fashion, art, sexuality, intellectual ideas, and adult behaviors and responsibilities (Siegel and Shaughnessy 1995). The heightened fascination with novelty in adolescence may represent an evolutionarily adaptive motivating force that facilitates learning. It has been suggested that in childhood play serves as a way to learn about real life experiences without actually participating in them so that the mistakes of learning do not produce damaging outcomes (Panksepp 1998a). In adolescence, the motivation to play progresses to a motivation for experimentation, reflecting intensified pursuit of novelty within the adult world. This experimentation is participation, arguably the most effective form of learning for a brain reaching maturity, but not without new risks that were absent in play. From the perspective of

an adult, decisions made in the naivete of adolescence may seem of poor judgment and actions may seem to be conducted impulsively. A sense of invulnerability is present in adolescence, and adolescents are prone to engage in behavior that puts them at risk for bodily harm, often minimizing their negative consequences (Clayton 1992).

An approach to understanding the relationship between adolescence and impulsive behaviors examines how the neural circuits mediating impulse control are changing during this stage of development. We review data suggesting that in adolescents as compared with adults promotional mechanisms are relatively hyperactive and inhibitory mechanisms relatively hypoactive.

Adolescent Neurodevelopment of Promotional Motivation Substrates

The appreciation for adolescence as a time of heightened novelty-seeking suggests that activity of brain regions involved in representing novelty and promoting motivated drives (Figure 3) more powerfully determines behavior in adolescents as compared with adults. As previously described, the NAc is a node within the PMC in which novelty is represented. In mammals, novel contexts invoke curiosity, manifesting as exploratory behavior and corresponding to DA release in the NAc, acting to signal novelty and serving as a "go" signal (Panksepp 1998b). For example, psychostimulants (like cocaine or amphetamine) or novel contexts can cause DA release in the NAc and provoke locomotor behavior in laboratory animals (Legault and Wise 2001; Piazza et al. 1989). Psychostimulants and environmental novelty can also synergize to produce hyperlocomotion (Badiani et al. 2000). DA neurons fire in response to novel stimuli and/or natural rewards, but, as the presentation of natural rewards become more predictable over repeated trials, DA cell firing diminishes (Waelti et al. 2001). Together, these findings suggest that during adolescence the high degree of novelty associated with many behaviors and situations may correspond with increased rates or effectiveness of DA cell firing within PMC.

Several lines of evidence suggest that adolescence is a period in which the mesolimbic DA system operates more robustly compared to the DA motivational system in mature adults. The increased incidence of Parkinson's disease (which becomes clinically evident upon loss of 90% of substantia nigra DA neurons) with age suggests that the DA system is at its most vigorous capacity of activity in early adulthood

(Cote and Crutcher 1991). Tic disorders, treated by agents that block central DA activity, are more prevalent in late childhood and early adolescence and tend to naturally diminish or remit in adulthood (Leckman and Cohen 1996). Experimentation with an addictive drug during adolescence is associated with a greater risk of addiction to that substance in adulthood possibly due in part to a mesolimbic DA system that is particularly vulnerable to pharmacological sensitization in the adolescent period of neurodevelopment (Johnson and Muffler 1997; Tsuchida et al. 1994).

Neurobiological data suggest that during neurodevelopment of adolescent monoamine systems, DA systems mature differently from 5-HT systems, leading to heightened motivational drive and/or impulsivity. CSF examinations of psychiatrically normal children and adolescents ages 1 to 16 reveal characteristic declines in concentrations of all the monoamines including 5-HT, its metabolite 5 hydroxyindoleacetic acid (5-HIAA), and the DA metabolite homovannilic acid (HVA) that asymptote at adult levels (Takeuchi et al. 2000). These declines in concentration may reflect an increase in CSF volume through which these products diffuse, concomitant with increases in the size of the ventricular system. However, over this period, there is also an increase in the ratio of HVA to 5-HIAA metabolites, suggesting that through adolescence the rate of DA turnover increases proportionally more rapidly as compared to that of 5HT (Takeuchi et al. 2000). In monkeys, the density of midbrain DA afferents onto PfC pyramidal neurons progressively increases from half of adult levels at 6 months of age to adult levels by 2 years of age (late adolescence in the monkey), at which time DA axonal input is roughly 3 times greater in number than 5-HT axonal input (Lambe et al. 2000). This contrasts with the developmental increase in 5-HT appositions onto PfC neurons which level off at adult levels by the second week after birth (Lambe et al. 2000). Since DA functioning is associated with the promotion of motivated drives while 5-HT activity may restrain engagement in impulsive behaviors, a widening difference in the overall robustness of DA system compared to the 5-HT system during adolescent neurodevelopment could underlie increased impulsivity.

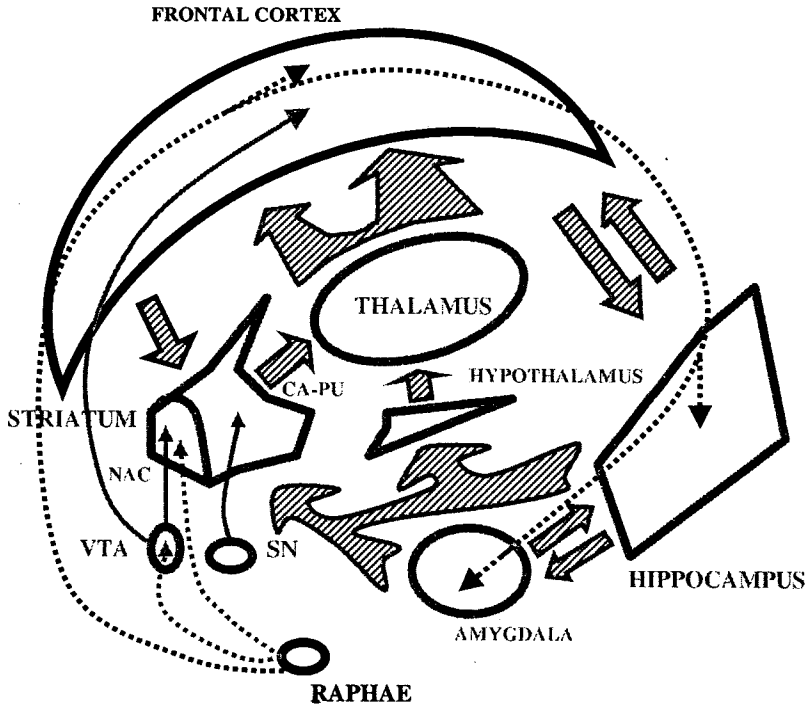
Several lines of evidence indicate that the hippocampus is involved in generating representation of novelty, possibly by regulating the amplitude or impact of DA discharge into the NAc (Legault and Wise 2001; Schmajuk et al. 2000). This aspect of hippocampal function is closely related to its role in storage and retrieval of contextual memory (McClelland et al. 1995). By comparing the immediate context with past memories of that context, the hippocampus can serve as a component of an environmental novelty detector system and influence motivational drive via regulation of NAc activity (Lorincz and Buzsaki 2000; Schmajuk et al. 2000). This notion is consistent with anatomical and physiological data showing that hippocampal damage alters quantitative DA release into the NAc and behavioral responses to novelty (Lipska et al. 1992; Lipska and Weinberger 1994).

The involvement of the hippocampal formation in regulating neural representations of novelty is salient to adolescent neurodevelopment. The hippocampal formation has prominent concentrations of sex hormone receptors that mediate powerful influences on neuroplasticity within this structure (Beyenburg et al. 2000; Shughrue and Merchenthaler 2000). Sex hormone receptors in the hippocampus and ventral striatum, as well as those in hypothalamic regions (that assist in regulation of striatal motivation systems), respond to surges in sex hormone levels during puberty, contributing to increased sexual motivation, sensitivity to novel sexual stimuli, sexual competition and adolescent aggression (Buchanan et al. 1992; Gorski 1999; Kirtzer 1997; Panksepp 1998c; Sizonenko 1978; Zarrow et al. 1969). The increase in sexual libido during adolescence may thus represent one component of a more generalized increase in novelty sensitivity and apparent impulsivity mediated by neurodevelopmental changes in SMC and PMC function. The extent to which differences in sex steroid regulation may in part account for differences in patterns of behaviors characterized by impaired impulse control is currently an active area of investigation.

Adolescent Neurodevelopment of Inhibitory Motivation Substrates

Evidence suggests that 5-HT and PfC function serve as principal impulse inhibition substrates in the brain (Figure 4). Studies of monoaminergic system described above suggest that in course of adolescence development, the inhibitory influence of the 5-HT system is proportionally less potent as compared with the pro-motivational DA system. Data also suggest that adolescence serves as time of profound change in the PfC. As such, the capacity of the PfC to inhibit impulses does not appear to be fully maximized until adulthood. This neuro-

Figure 4
Inhibitory Motivational Substrates, Shown in Bold, Are Involved in the Inhibition and Decision-Based Control of Motivated Drives



Note: Data indicate that compromise of these systems produces increased impulsivity. Serotonin modulation of motivational and action-oriented decision-making circuitry originating from raphae nuclei has been associated with regulation of aggressive impulses and pursuit of natural rewards. Frontal/prefontal cortex, via connections with SMC components and subcortical promotional motivation circuitry, is involved in the representation, executive control and inhibition of motivated drives.

developmental process may serve as a normal, necessary and even advantageous condition of adolescent development; however it may also place adolescents at increased risk for a variety of disadvantageous behaviors characterized by impaired impulse control.

Mental performance dependent on the PfC, such as working memory, complex problem solving, abstract thinking, and sustained

logical thinking, improves markedly in humans and other primates during adolescence (Feinberg 1983; Flavell 1963; Woo et al. 1997). Direct measures of the capacity to inhibit simple psychomotoric responses show a progressive improvement through childhood, reaching a maximum capability at about age 17 and exhibiting a slow decline into old age (Williams et al. 1999).

Profound changes in physiological measures of cortical function also take place during adolescence. Childhood and adolescence is the period of greatest change in sleep EEG (electroencephalogram) readings: the time spent in Stage 4 non-REM (non-rapid eye movement or slow wave) sleep declines by about 50% and delta wave amplitude decreases by approximately 75%, at which level it remains throughout adult life (Feinberg 1983; Feinberg et al. 1977). In late childhood and early adolescence, the latency of event related potentials (ERP, the time between a salient sensory event and a positive wave deflection in the EEG) also declines by about 70% to adult levels (Courchesne 1977; Goodin et al. 1978).

Anatomical brain changes are also evident in adolescent neurodevelopment. Neuroimaging reveals that from ages 6 to 12, the ratio of lateral ventricle to brain volume remains constant, while this ratio increases steadily from ages 12 to 18 (Giedd et al. 1996). Meanwhile, from ages 4 to 17 there is a continuous increase in white matter density in frontal cortical regions, probably due to increased myelination of neurons and axonal diameters (Paus et al. 1999). This myelination process increases speed and efficiency of action potential propagation throughout the cortex and likely contributes to neurophysiological and cognitive changes observed through adolescence (Paus et al. 1999).

Normal neurodevelopment from birth to adulthood is also correlated with changes in local and total brain metabolic rates, which may profoundly influence patterns of brain function and information processing. From birth, structures throughout the brain show an increase in energy usage concentration reaching adult levels by age 2, rising up 2-fold greater than adult levels by age 9, then declining back down to adult levels by the end of adolescence (Chugani et al. 1987; Kety 1956). Regional variations in this developmental theme are notable: cortical areas undergo a greater rise and fall of metabolic rates over time and undergo these changes at later ages compared to subcortical regions (Chugani et al. 1987). Further, frontal cortical regions tend to undergo these transitions lastly (Chugani et al. 1987).

Developmental transitions in metabolic activity parallel neuroplastic changes in the: 1) density of dendritic processes, synapses, and myelination; 2) rate of neuronal membrane synthesis; and, 3) emergence of adult cognitive styles (Lewis 1997; Minshew et al. 1992; Nudo and Masterson 1986; Paus et al. 1999; Spinelli et al. 1980; Yakovlev and Lecours 1967). Electron microscopy of layer III of human PfC reveals that synaptic density increases to 17×10^8 per cubic mm between ages one and 5, then declines to adult levels of 11×10^8 per cubic mm by late adolescence (Huttenlocher 1979). Declines in metabolic activity in frontal and other cortical regions during adolescence may reflect synaptic pruning or reductions in synaptic density, whereby competition between neuronal connections selectively reduce energy-consuming synapses that do not efficiently transmit information relevant to past experience. These histological changes also correlate with gross anatomical changes. Recent magnetic resonance imaging studies have revealed that dorsolateral PfC undergoes developmental changes during adolescence during which its total size relative to other brain regions increases while its density of gray matter decreases (Sowell et al. 2001). Observed in general in cortical regions, this developmental pattern is most pronounced in the PfC and likely corresponds to synaptic pruning (reducing cortical gray density) concomitant with greater myelination of large axonal tracts projecting into and out of the PfC (increasing total volume) (Sowell et al. 2001).

Neural network simulations suggest that the rise of cortical interconnectivity during childhood, followed by a decline to adult levels over adolescence, could reflect evolutionarily-determined optimization of learning capacity according to the developmental stage (Spitzer 1999; Woo et al. 1997). When little is known about the environment, it is advantageous for the organism to learn rapidly, which is made possible by high rates of neuroplasticity. As accumulating information about the environment is stored in connections within neural networks, learning rates, or the capacities for neuroplasticity, decrease, resulting in a system that operates to prevent loss of previously-learned information (Spitzer 1999). A fundamental property of neural networks involves a trade-off between the capacity to learn new information vs. capacity to utilize information that has already been learned (Spitzer 1999). As such, it is important for an organism to regulate the degree of neuroplasticity within a system appropriate for specific stages of development in order to optimize functioning of these neural networks (Spitzer 1999).

Detailed analysis of neuroanatomical changes during adolescence in monkeys suggests that synaptic pruning also occurs within specific components of cortical microarchtecture impacting in specific ways upon information processing (Lewis 1997). Reductions in axo-dendritic connections in layer III of PfC is much greater for connections that arise primarily from proximal cortical regions rather than distant association cortices (Woo et al. 1997). Increases in the ratio of long-range to local cortical connectivity during adolescence suggests that frontal regions progressively rely more on 'top-down processing' in which highly-processed multimodal information representing an increasingly large and sophisticated repertoire of past experiences has increased computational influence (Lewis 1997). Thus, as the cognitive and perceptual understanding of the environment becomes increasingly rich and abstract, decision-making may incorporate information from an increasingly sophisticated memory base. Cortical pruning in adolescent monkeys is also associated with decreases in markers of both excitatory and inhibitory inputs to cortical pyramidal neurons (Anderson et al. 1995). Neural network simulations suggest that counterbalanced reductions in excitatory and inhibitory inputs can increase the stability of pyramidal neuron's firing patterns (Rutherford et al. 1998) and enhance the capacity for local ensembles of PfC cortical neurons to fire in a sustained, concerted manner (Lewis 1997; Miller 1996). This capacity may underlie, in part, the ability of frontal cortical regions to 'hold information on-line until a best possible decision is made.' For instance, improved performance of monkeys on a delayed response task during adolescence corresponds to an increase in the percentage of neurons in the PfC that show sustained activity during the delay period of the task (Alexander 1982).

Taken together, these findings indicate frontal cortical maturation is a key process in adolescent neurodevelopment. Rapid learning about the environment in childhood is made possible by a heightened capacity for neuroplasticity, incurred at a cost to resources that could otherwise be used to store accumulating memory, provide for the complexity of memory, and increase the speed of information processing. Cortical pruning during adolescence underlies a shift favoring these latter processes. It allows the PfC to hold on line and process an increasingly large number and sophisticated array of neural representations of cause-and-effect relationships in the environment, influenced by internalized representations of past experiences. Thus, experiential understanding of environmental stimuli become increasingly abstract

and nuanced, enhancing the capacity for contingency-planning and prediction-making. As the neural architecture of the PfC matures to accommodate these abilities, its input to subcortical motivational structures also becomes more substantial and complex, resulting in an overall increase in the activity of the PfC to inhibit motivational drives that might otherwise be enacted 'impulsively.'

SUMMARY

This review explores an association between gambling behaviors and impulsivity in adolescents within the context of neurodevelopmental changes in brain structure and function. An operationalized understanding of impulsivity defines it in terms of the regulation of the enactment of motivated drives associated with brain processes underlying risk-benefit assessment. Gambling can be viewed as involving repeated participation in ritualized 'impulsive' decision-making. Neurobiological data allows a characterization of many aspects of the anatomy and function of brain structures involved in motivation and impulsive behavior. These data suggest that the promotion of the enactment of motivated drives, relevant to their potential benefits as encoded within brain circuitry, involves mesolimbic DA systems. 5-HT systems and the PfC are more directly involved with appropriate selection and inhibition of motivated drives. Psychiatric conditions associated with the enhancement of substrates that promote motivated drives, compromise of substrates that inhibit motivated drives, or disruption of substrates involved in decision-making per se appear characterized by increased impulsivity. A review of data pertaining to the neurodevelopment of motivational circuitry in adolescence indicates that in the adolescent brain relative to the adult brain, impulse-promoting substrates operate more robustly while those that inhibit impulse or appear involved directly in decision-making are not yet maximized. Specifically, mesolimbic DA function underlying promotion of motivational drives reaches maximal functioning prior the full implementation of frontal cortical inhibitory potential. These circumstances do not necessarily represent abnormalities or forms of mental illness. In fact, they reflect brain form and function that optimizes experiential opportunities and learning mechanisms appropriate to the neurodevelopmental stage of the individual. However, they suggest that the adolescent stage of neurodevelopment imparts a biological vulnerability to problem gambling,

PG, and other behaviors and disorders characterized by impaired impulse control.

Given the complexities of actions influenced or encompassed by impulse control, decision-making and gambling, it is expected that the proposed developmental model of neurocircuitry will not completely account for all aspects of adolescent problem or pathological gambling. Rather, the proposed model is meant to serve as a useful foundation on which to examine empirically aspects of impulse control, decision-making and problem and pathological gambling vulnerability within a neurodevelopmental context. More research is needed to investigate directly the proposed neural circuits in animal models and humans and determine potential mediating roles for these circuits in specific gambling behaviors in specific stages of development. As brain imaging techniques continue to be refined to study adolescent populations (Peterson 1995; Filipek et al. 1994; Makris et al. 1999), direct examination of these hypotheses in humans seems a likely prospect in the near future. Further study of gambling behaviors in adolescent populations is needed to confirm the presence of a uniquely heightened vulnerability in this age group. Methods characterizing general traits of impulsive decision-making should also be used to compare adolescents with other age groups. As the knowledge of the biological mechanisms underlying PG at specific life stages grows, it is hopeful that the improved understanding can be efficiently translated into clinically-relevant advances. The findings presented in this review highlight the need for translational research guiding the development of prevention and treatment interventions specific for adolescents with problem gambling or PG. Such strategies may include psychoeducational or pharmacological approaches that serve to modulate neurotransmitter systems influencing activity in primary and/or secondary motivation circuitry.

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Advances in the Pharmacological Treatment of Pathological Gambling

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In the present paper we discuss the current status of drug treatment for pathological gambling and the scientific rationales underlying the various pharmacological approaches. Specifically, we summarize the treatment study results of serotonin reuptake inhibitors, mood stabilizers, opioid antagonists, and atypical antipsychotics in pathological gambling. We also discuss dosage strategies, the duration of treatment, issues surrounding medication compliance, and approaches to treatment-refractory pathological gambling, such as pharmacological and behavioral augmentation.

KEY WORDS: pathological gambling; impulse control; psychopharmacology.

Pathological gambling, a disorder characterized by persistent and recurrent maladaptive patterns of gambling behavior, was first designated a psychiatric disorder in 1980 in the third edition of the Diagnostic and Statistical Manual (DSM-III), and in the revised edition (DSM-III-R) was grouped under the category "disorders of impulse control not elsewhere classified" (American Psychiatric Association

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