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Recent Research on Impulsivity in Individuals With Drug Use and Mental Health Disorders: Implications for Alcoholism

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Abstract

Alcohol misuse and dependence, and many of its accompanying psychological problems, are associated with heightened levels of impulsivity that both accelerate the development of clinically significant illness and complicate clinical outcome. This article reviews recent developments in our understanding of impulsivity as they relate to brain circuitry that might underlie these comorbid factors, focusing upon the clinical features of substance use (and dependence), bipolar disorder, and pathological gambling. Individuals who are affected by these disorders exhibit problems in several domains of impulsive behavior including deficient response or “motor” control, and the tolerance of prolonged delays prior to larger rewards at the expense of smaller rewards (“delay-discounting”). These populations, like alcoholic dependents, also exhibit impairments in risky decision-making that may reflect dysfunction of monoamine and catecholamine pathways. However, several areas of uncertainty exist including the specificity of impairments across disorders and the relationship between impulse control problems and altered evaluation of reward outcomes underlying observed impairments in action selection.

Keywords

Impulsivity; Substance Misuse; Alcohol; Pathological Gambling

THE DEVELOPMENT AND course of alcohol use and dependence is complicated by heightened impulsivity (Dom et al., 2006; Miller, 1991). Impulsivity appears to moderate alcohol-seeking behavior, relapse, and eventual clinical outcome (Noel et al., 2007). Reviews have noted that impulsivity encompasses a wide range of relatively normal, non-pathological aspects of function, and maladaptive behaviors that are relevant to clinical order (Cardinal et al., 2004; Dickman, 1993; Evenden, 1999b; Soloff et al., 2003). However,

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The subject of this mini-review was presented at a symposium held by the Internal Society for Research on Impulsivity (ISRI) at the Scientific Meeting of the Research Society on Alcoholism (RSA) in San Diego on June 9, 2009. The organizer and chair of the symposium was Professor Marc Potenza. The speakers were Professors Gerry Moeller, Alan C. Swann, Luke Clark, and Robert D. Rogers.

as a clinical construct, impulsivity has been variously defined as swift action without forethought or conscious judgment (Hinslie and Shatzky, 1940), or the tendency to act with less forethought than individuals of equal ability or knowledge (Dickman, 1993).

While research continues into the psychometrics of impulsive behavior (Cloninger, 1987; Patton et al., 1995; Weijers et al., 2001) and its fractionation into subtypes that reflect distinct underlying cognitive, emotional, and neural processes (Barratt, 1965; Evenden, 1999b; Moeller et al., 2001a; Patton et al., 1995), our wider understanding of impulsivity remains seriously under-developed. However, this situation is now changing rapidly in ways that will benefit our understanding of the presentation and treatment of alcohol and substance use disorders. In this review, we focus upon those aspects of impulsive behavior that seem most relevant to understanding clinical illnesses.

First, as detailed elsewhere in this volume (Winstanley et al. [this volume]), animal models provide an increasing precision of information about the neuropsychology of impulsive behaviors (Cardinal, 2006; Dalley et al., 2008; Pattij and Vanderschuren, 2008; Winstanley et al., 2006a). This research has tended to concentrate upon “motoric” forms of impulsivity, involving individual variability in the capacity to modulate (or withhold) primed or initiated behaviors, and the tendency to opt for smaller, sooner rewards at the expense of larger, later rewards as instantiated in “delay discounting” paradigms. A small amount of research with rats has also addressed the capacity of individuals to gather all of the necessary information before selecting an appropriate response in the form of “reflection” impulsivity, with a focus upon the role of serotonin (Evenden, 1998a).

Dissociations in the neuropsychology of animal models also help to cross-validate distinctions between different forms of impulsive behavior as proposed within the human literature. Thus, while lesions of the orbitofrontal cortex produce complex changes in animals’ sensitivity to delays prior to smaller and larger rewards depending upon previous learning (Mobini et al., 2002; Winstanley et al., 2004b), lesions of the anterior cingulate cortex (and its medial prefrontal surround) influence the capacity to withhold responses in situations where participants are required to wait for an imperative stimulus (Chudasama et al., 2003) [although the anterior cingulate cortex also plays a significant role in wider aspects of reward-based learning and decision-making (Rudebeck et al., 2006)]. Such experiments delineate an overlapping fronto-striatal circuitry in which different neural stations play complementary roles in impulse control functions (e.g., the anterior cingulate vs. orbitofrontal cortex), while other nuclei (e.g., subthalamic nucleus) contribute to both delay-discounting mechanisms and simpler inhibitory functions (Baunez and Robbins, 1997; Uslaner and Robinson, 2006; Winstanley et al., 2005). These dissociations mirror evidence that different forms of impulsive control (e.g., delay-discounting and response control) involve distinct serotonergic receptor systems (Evenden, 1998b, 1999a; Winstanley et al., 2004a), as well as complex interactions with dopamine activity, most notably mesolimbic pathways involving the ventral striatum (Winstanley et al., 2003, 2006b).

Animal models of impulsivity also help us to understand the phenotypic presentation of clinical disorders, as well as the mechanisms of putative treatments. To take one example, the heightened delay-discounting and premature operant responding associated with reduced

levels of D₂ receptor expression within the core of the nucleus accumbens goes along with heightened self-administration of cocaine (Dalley et al., 2007a; Economidou et al., 2009). This suggests that the impulsivity trait that promotes both drug-seeking behavior in human substance users and clinical relapse in dependent individuals is mediated by striatal D₂, though not D₁, activity (Volkow et al., 2004).

Impulsivity, as it relates to a loss of behavioral control specifically, is also a prominent feature of attention deficit hyperactivity disorder (ADHD) and is readily observed in rat models of the condition (Russell et al., 2000). Schachar and colleagues (2001) have provided a useful distinction between “action restraint” that describes the inhibition of the motor behavior before it has been commenced, and “action cancellation” that describes the suppression of motor behavior during its execution (Schachar et al., 2001). Action restraint relates to concepts of motoric and, perhaps, attentional impulsivity identified by psychometric investigations (Barratt, 1993; Patton et al., 1995) and is reflected in the performance of successive discriminations paradigms such as Go/No Go and continuous performance tasks. By contrast, action cancellation relates more directly to the modulation of already-initiated behaviors at later stages of motor output and is studied using paradigms such as the Stop-Signal task (Eagle et al., 2008).

Experimental investigations suggest that action restraint and cancellation are probably mediated by overlapping, but subtly dissociable fronto-parietal cortical networks (Rubia et al., 2001, 2003), and that serotonin and catecholamine neuromodulators influence these aspects of control in different ways (see Eagle et al., 2008 for detailed review). In testing for mechanisms that might be implicated in ADHD, atomoxetine, the noradrenaline reuptake inhibitor approved for the treatment of ADHD, has been shown to improve action cancellation, as the inhibition of already-initiated actions (Bari et al., 2009; Chamberlain et al., 2006; Navarra et al., 2008), perhaps via its action within the human inferior right prefrontal cortex (Chamberlain et al., 2009). This cortical area is an important node in a distributed circuit connecting the anterior cingulate cortex and subthalamic nucleus; the latter playing a role in the inhibition of activated motor output (Aron, 2007). By contrast, manipulation of serotonergic activity including the selective serotonin reuptake inhibitor, citalopram, has only limited beneficial effects on this manifestation of action control in the rat (Bari et al., 2009; Chamberlain et al., 2006).

In humans, atomoxetine has also been shown to improve Stop-Signal task performance but not probabilistic reinforcement learning, while the selective serotonin reuptake inhibitor, citalopram, influences probabilistic reinforcement learning but not Stop-signal task performance, indicating a double dissociation between action cancellation and this form of learning (Chamberlain et al., 2006). However, noradrenaline may also play a role in certain forms of impulse control. This is evidenced by findings that administration of atomoxetine to rats can increase choices of large, delayed rewards in a delay-discounting task (Bari et al., 2009). In summary, distinct manifestations of impulsivity depend, to some degree, upon the actions of different neuromodulators that may form targets for therapeutic interventions in clinical groups (Winstanley et al., 2006a).

The second important feature of current research is the focus upon how impulsivity is manifested in clinical populations, its relationships with underlying pathophysiology, and its associations with illness vulnerability and relapse (Clark et al., 2006; Mitchell et al., 2005; Verdejo-Garcia et al., 2008). Substance users exhibit impairments in go-no-go performance (as action restraint) (Verdejo-Garcia et al., 2006) and steeper delay-discounting functions when compared to control participants (Bickel and Marsch, 2001). However, the degree of impulsivity exhibited may also express some of the state specificity in these disorders; for example, impulsivity (as delay-discounting) may be exacerbated in nonabstinent cigarette smokers compared to abstinent individuals (Bickel et al., 1999). Investigations into impulsivity in alcoholism demonstrate many features described previously: alcoholic individuals show an association between motor impulsivity and P300 signals within the anterior cingulate cortex, perhaps reflecting its role in action control (Chen et al., 2007; Mitchell et al., 2005), while the same patients also show impairments in delay-discounting (Mitchell et al., 2005), and at least some of these impairments appear to reflect some familial vulnerability (LeMarquand et al., 1999).

Understanding how impulsivity makes a difference to alcoholism is complicated by its high co-morbidity with other mental illness (Kuo et al., 2008; McIntyre and Keck, 2006), perhaps reflecting common aspects of pathophysiology (Slutske et al., 2000). This mini-review provides a brief overview of the impact of impulsivity in 3 such disorders: cocaine use and dependence, bipolar disorder, and pathological gambling. We also consider the involvement of related impairments in risky decision-making in these patient populations.

IMPULSIVITY AND DECISION-MAKING IN COCAINE DEPENDENCE

Over the last 10 years, there has been recognition that chronic cocaine use is associated with several cognitive deficits. One prominent feature of these deficits is impulsivity. Impulsivity, in this context, can be thought of as a predisposition toward rapid unplanned reactions to internal or external stimuli without regard to the negative consequences (Moeller et al., 2001a). In this definition, there is a clear overlap with the construct of addiction, which has been defined as “the loss of control over the intense urges to take the drug even at the expense of adverse consequences” (O’Brien et al., 2006).

Given that the comprehensive characterization of impulsivity requires the use of a battery of instruments (Barratt, 1993; Moeller et al., 2001a), investigations into impulsivity have tended to use multiple measures, both psychometric and laboratory, performance-based tests. Accordingly, cocaine-dependent individuals have shown heightened scores on questionnaire, as well as behavioral measures of impulsivity. Specifically, studies have consistently shown that cocaine-dependent individuals have higher scores on the Barratt Impulsiveness Scale (BIS) (Moeller et al., 2002; Patkar et al., 2004); worse performance on measures of behavioral inhibition/(action restraint) such as continuous performance test (Moeller et al., 2004, 2005) and go-no-go tasks (Lane et al., 2007). Cocaine users also perform more impulsively on measures of delay-discounting involving choices between smaller, sooner rewards and larger, delayed rewards (Allen et al., 1998; Moeller et al., 2002; Petry and Casarella, 1999a). Impulsivity in cocaine users and cocaine dependents also has

implications for treatment, in that higher impulsiveness is associated with poorer treatment response (Moeller et al., 2001b; Patkar et al., 2004).

Cocaine dependence also seems to involve impaired decision-making. Decision-making involves the outcome of cognitive processes leading to a choice between alternative courses of action. Poor decision-making has been described as “deciding against one’s best interests and inability to learn from previous mistakes, with repeated decisions leading to negative consequences” (Bechara and Damasio, 2005). A widely used, and neurologically sensitive, measure of decision-making is the Iowa Gambling Task (IGT) (Bechara et al., 1994). The IGT was developed by Bechara and colleagues to measure decision-making in patients with focal brain injury, who made poor choices, leading to negative consequences in spite of having otherwise intact intellectual function. Patients with focal ventromedial prefrontal cortical injuries made consistently poor choices on the IGT, which paralleled their real life, postlesion functional problems (Bechara et al., 2000).

Similar to brain lesion patients, cocaine-dependent individuals also show a preference for disadvantageous choices on the IGT. Stout and colleagues (2004) found that cocaine-dependent participants preferred the disadvantageous choices relative to controls. Cognitive modeling suggests that motivational and choice consistency factors, but not learning and memory, are responsible for the decision-making deficit in cocaine users (Stout et al., 2004). Verdejo-Garcia and colleagues (2007) compared IGT performance between 12 abstinent cocaine-dependent subjects and 14 controls, finding that cocaine-dependent individuals showed poorer performance on the IGT that correlated with amount of past cocaine use (Verdejo-Garcia et al., 2007). In a recent report (van der Plas et al., 2008), cocaine, methamphetamine, and alcohol-dependent men and women were compared to controls using the IGT. This study showed fewer advantageous choices with methamphetamine and cocaine-dependent individuals. Finally, those individuals with poorer decision-making on the IGT had worse treatment response (Green et al., 2009a).

Impulsive behavior in cocaine dependence is associated with functional brain abnormalities as revealed by functional magnetic resonance imaging (fMRI) investigations. Kaufman and colleagues (2003) used fMRI to compare cocaine users and controls during the performance of a go-no-go task. Results showed significantly lower activation of anterior cingulate and right insula in cocaine users for successful inhibitions (STOPS) on no-go trials relative to go trials. In addition, cocaine users showed significantly lower activation in the anterior cingulate as well as right medial frontal gyrus, presupplementary motor area, left insula, and left inferior frontal gyrus for failed inhibitions (ERRORS) on no-go trials relative to go trials (Kaufman et al., 2003). In another study using a go-no-go task, but this time involving variable working memory demands, cocaine users showed reduced signal within the anterior cingulate and right prefrontal cortex compared to controls for the group by working memory load interaction for successful response inhibitions relative to go trials (Hester and Garavan, 2004). Although this study did not report the contrast of no-go with go trials, which would test for specific signals in behavioral inhibition, the authors did report a significant positive correlation between anterior cingulate activity and correct inhibitions on the no-go trial, supporting a role for this brain region in action restraint (Hester and Garavan, 2004).

Decision-making has also been studied in cocaine-dependent subjects using fMRI. Bjork and colleagues (2008) compared neural signals in a heterogeneous group of drug-dependent individuals and controls while performing a risk-taking task. Guaranteed reward activated the head of the caudate in drug-dependent participants but not in the controls. The predecision signal in the posterior mesofrontal cortex was also blunted in drug-dependent participants compared to controls, suggesting that substance dependence is characterized by a combination of striatal hypersensitivity to reward and reduced recruitment of conflict monitoring circuitry when reward is associated with potential penalties (Bjork et al., 2008). Another study (Goldstein et al., 2007a) used fMRI to compare cocaine-abusing individuals and controls in response to gradients of monetary rewards. Cocaine abusers showed reduced regional signal to differences between across the reward gradient, and that prefrontal cortex sensitivity to money was associated with motivation and self-control within cocaine abusers but not controls. A second study by the same group showed that lower subjective sensitivity to reward gradients significantly correlated with enhanced signals to monetary reward in the lateral orbitofrontal cortex, inferior frontal gyrus, and amygdala, but smaller signals along the middle frontal gyrus in cocaine abusers (Goldstein et al., 2007b). These studies suggest that cocaine use involves altered activity within frontal-striatal circuits modulated by dopamine (Clark et al., 2004).

At the current time, we know very little about the structural changes that might mediate the differences in impulsivity and risky choice between cocaine users and nonusing controls. However, some of the deficits described previously appear to relate to white matter integrity as measured by diffusion tensor imaging (DTI). Moeller and colleagues (2005) report that cocaine-dependent individuals exhibited reduced fractional anisotropy (FA) in the anterior corpus callosum compared to controls. Within the cocaine dependents, the reduction in FA significantly correlated with errors of commission on a continuous performance test (Moeller et al., 2005). In addition, cocaine abusers showed increased radial diffusivity, which has been associated with altered myelin in animal studies (Moeller et al., 2007). The same authors, using a different sample of cocaine dependents, have replicated the finding of reduced FA in the corpus callosum in cocaine abusers and shown that severity of drug use is related to reduction in FA (Ma et al., 2009).

These results have been supported by other evidence suggesting a reduction in FA of the corpus callosum and internal capsule of cocaine users, with the reduction correlating with impulsivity as measured by the BIS (Lim et al., 2002, 2008). Animal data suggest that the lower FA may be related to cocaine use. Narayana and colleagues (2009) administered cocaine or saline chronically via an osmotic minipump to rats. The cocaine-treated rodents were found to have significantly lower FA and radial diffusivity in the splenium of the corpus callosum compared to saline-treated rats. The cocaine-treated rats also had lower myelin basic protein and higher neurofilaments compared to saline-treated rats. Therefore, at least some of the DTI-related changes in white matter seen in cocaine users may be because of chronic cocaine administration.

To summarize, alcoholism is common in cocaine abusers (Carroll et al., 1993). In samples of individuals identified on the basis of cocaine use, there is consistent evidence of elevated impulsivity and impaired decision-making. These cognitive deficits are associated with poor

treatment outcome and alteration in brain function and structure as identified using fMRI and DTI. There is also preliminary evidence that at least some of the white matter changes are directly related to chronic cocaine use. Future studies on the neurobiology of impulsivity in cocaine dependence should determine whether treatments can protect against, or reduce, neuronal changes and the associated cognitive impairments in cocaine users and lead to improved clinical outcome in these individuals.

IMPULSIVITY AND DECISION-MAKING IN BIPOLAR DISORDER

Impulsivity, related to the action restraint, is a core component of bipolar disorder (McElroy et al., 1996). It is also prominent in mania, and impulsive behavior is required to meet DSM-IV criteria for hypomanic or manic episodes.

A number of investigations have found that BIS-11 scores are elevated in patients with bipolar disorder compared to controls (Swann et al., 2009a). Despite its modest correlation with affective state (Swann et al., 2008), BIS-11 scores have also been found to be higher in euthymic subjects with bipolar disorder compared to controls, suggesting that impulsivity is a predisposing trait for the disorder (Swann et al., 2003). Residual BIS-11 scores after regression on depressive and manic symptoms also differ significantly between individuals with bipolar disorder and controls (Swann et al., 2009a). Impulsivity relates to aspects of the disorder's course in that BIS-11 scores have been found to be higher in patients who had early onset of illness, many depressive or manic episodes, history of a substance- or alcohol-use disorder, and history of suicide attempts, compared to patients with bipolar disorder without these characteristics (Swann et al., 2009a). (As expected, individuals with bipolar disorder lacking these characteristics still had significantly higher BIS-11 scores than healthy control subjects.)

The manifestation of impulsivity in bipolar disorder involves some of the problems with response inhibition/action restraint observed in alcoholic patients (Easton et al., 2008). Swann and colleagues (2009b) report that patients with bipolar disorder made fewer correct detections during performance of the continuous performance task, indicative of reduced attention, reduced accuracy, and slower reaction times. These aspects of performance were taken as difficulty in organizing a delayed response, or as a result of a compensatory mechanism whereby errors of commission are reduced at the cost of slower responses. Reaction times were, however, faster in patients with highly recurrent illness or history of alcohol- or substance-use disorders than in patients with bipolar disorder without these features, suggesting failure of this compensatory mechanism. These abnormalities persisted across affective states and were present regardless of pharmacological treatment (Swann et al., 2009b).

Problems with impulsive behavior in bipolar disorder also extend to delay-discounting. Using the Single-Key Impulsivity task (SKIP), a free-operant-responding task where participants are rewarded for delaying responses, individuals with bipolar disorder made more responses than controls, and had a shorter maximal inter-response delay. These characteristics appear to be independent of affective state or treatment (Swann et al., 2009b). This deficit was also found to be increased in a group of manic patients and in a group with

both manic and depressive symptoms when compared to controls (Strakowski et al., 2009). Probit analysis of the dataset showed that rapid responding on the continuous performance task and rapid responding on the SKIP (at the expense of reward) were associated with the number of manic or depressive episodes, and with history of a substance- or alcohol-use disorder. This suggests that impulsivity is indicative of a sensitized course of bipolar disorder; or that impulsive characteristics could precede illness, as part of a predisposition to severe bipolar disorder (Swann et al., 2009b).

Observations of elevated impulsivity in bipolar disorder raise the issue of whether behavioral control is further compromised by state factors in manic episodes of the illness or the more frequently experienced periods of depression. Psychometric assessments suggest that attentional and motor impulsivity, as measured by the BIS-11 (Barratt, 1993), are increased in manic episodes and show a significant association with SADS-C Mania factor scores (Swann et al., 2008). The symptoms correlating most strongly with impulsivity may be visible hyperactivity > increased energy > accelerated speech; with no correlation involving subjective mood. Manic symptoms are also often present during predominately depressive episodes. Manic symptom ratings in bipolar depressive episodes correlate with impulsivity and with clinical indices of a severe course of illness including early onset, histories of alcohol-use disorders, and suicide attempts, bridging state-related and trait-related aspects of the disorder (Swann et al., 2008).

Elevated attentional and nonplanning impulsivity, as scored by the BIS-11, have been observed during depressive episodes and correlate with depressed mood; impulsivity also correlates with hopelessness, anhedonia, and suicidality (Swann et al., 2008). In this way, impulsivity may interact with depression to increase the risk of suicide. Simon and colleagues (2001) reports that medically severe impulsive suicide attempts were more likely to involve violent methods even though actual suicidal intent was milder than in planned attempts. This reflects the dissociation between behavior and conscious intention that characterizes impulsivity. Impulsive attempters were less likely to be depressed, but equally likely to experience hopelessness, compared to nonimpulsive attempters. This is consistent with the characteristics of impulsivity as reflected by the subscales of the BIS-11 score: lack of capacity for cognitive complexity (attentional impulsivity) leading to poor problem solving and low resilience, and a lack of sense of the future (nonplanning impulsivity) (Stanford et al., 2009). Among individuals with diagnoses of bipolar disorder, elevated BIS-11 scores and rapid-response impulsivity were associated with a history of having made a suicide attempt. Severity of the most recent past attempt was related to rapid-response behaviors, but not BIS-11 scores (Swann et al., 2005b).

Finally, there is some evidence to suggest that the state-dependent changes in impulse control function in bipolar disorder involve altered catecholamine and, in particular, altered noradrenaline activity. As noted previously, administration of atomoxetine has been shown repeatedly to modulate action cancellation as measured in the Stop-Signal task (Bari et al., 2009; Chamberlain et al., 2006, 2007; Eagle et al., 2008; Schachar et al., 2001). Other data have shown comparable results following desipramine treatment (Overtoom et al., 2003). Noradrenaline has a profound influence on the cognitive functions of the prefrontal cortex function mediated by a balance of α -1 and α -2 adrenoceptor activity (Arnsten et al., 1999).

Under conditions of extreme stress, excessive stimulation of α -1 adrenoceptors can impair prefrontal cortical cognitive activity. Other situations that elicit noradrenaline release, such as manic states in bipolar disorder, can have the same effect (Swann et al., 1987). Severity of manic symptoms has been found to correlate with noradrenaline metabolite concentrations in cerebrospinal fluid (Swann et al., 1987) and various laboratory measures of impulsivity (Swann et al., 2001). Stimulation of noradrenaline release by the nonselective α -2 adrenoceptor antagonist, yohimbine, also increases laboratory-measured impulsivity in the form of errors of commission during an adapted continuous performance test in healthy controls (Swann et al., 2005a). Atomoxetine may also reduce impulsive behaviors in the form of choices of smaller, sooner rewards in delayed discounting (Bari et al., 2009).

Repeated catecholaminergic stimulation, by stressors, stimulants, or, potentially, mania, may lead to persistently enhanced motor and motivational responses to catecholamines (Drouin et al., 2002) and this may underlie the recurrent course of bipolar disorder. Behavioral sensitization is a potential mechanism by which a recurrent course of bipolar disorder, or bipolar disorder complicated by stressors or substance use disorders, could lead over time to more severe impulsivity even outside of manic episodes and in the euthymic state (Dienes et al., 2006). Therefore, sensitization to the effects of catecholamines may increase impulsivity. Altered noradrenergic function may also underlie the inability to sustain attention in the euthymic state that might itself constitute a vulnerability marker in affected individuals (Clark et al., 2002).

To summarize, impulsivity, involving poorly regulated action, is pervasive in bipolar disorder and may be one of the basic mechanisms of the illness. It has a state-dependent component that correlates differentially with depressive or manic symptoms. This is superimposed on trait-like features that include the integrated impulsivity reflected in total scores of the BIS-11, problems with response inhibition, and problems with tolerating delays before responding for rewards. There is also some evidence that these features of the disorder involve increased sensitivity to catecholamine activity.

IMPULSIVITY AND DECISION-MAKING IN PATHOLOGICAL GAMBLING

Pathological gambling is a DSM-IV-TR Impulse Control Disorder that is viewed increasingly as a “behavioral addiction.” As with alcohol dependence, pathological gamblers display several hallmarks of an addiction syndrome, including symptoms of withdrawal, tolerance, and cravings (Shaffer et al., 2004), and there is substantial co-morbidity between pathological gambling and substance use disorders (Potenza, 2006).

Impulsivity is a prominent feature of pathological gamblers. Numerous studies have reported elevated scores on a constellation of impulsivity-related traits measured using psychometric instruments, including sensation seeking and novelty seeking (Castellani and Rugle, 1995; Cunningham-Williams et al., 2005; Kim and Grant, 2001; Lawrence et al., 2009b; McCormick et al., 1987). In a recent study, Lawrence and colleagues (2009a) observed significant increases on the BIS-11 and the Adult ADHD Self-Report Scale (ASRS) (Kessler et al. 2004) in both problem gamblers and individuals with alcohol dependence. These elevated scores were increased to greater extent than the *compulsivity*

scores as measured by the Padua Inventory, a measure of subclinical obsessive compulsive disorder (OCD) symptoms. While earlier studies have reported significant increases on other compulsivity scales in pathological gamblers (Blaszczynski, 1999; Frost et al., 2001), a recent study conducted by Blanco and colleagues (2009) examined the relationship between gambling symptoms, impulsivity, and compulsivity in 38 pathological gamblers who were participating in a trial of the selective serotonin reuptake inhibitor, paroxetine. The correlation between gambling severity and compulsivity did not withstand statistical control for impulsivity, and the improvement in gambling severity following paroxetine treatment was best predicted by impulsivity rather than compulsivity. Thus, while both impulsive and compulsive features are detectable in pathological gamblers, impulsive features seem to predominate and are more closely associated with the severity of gambling problems (Blanco et al., 2009).

Impulsivity scores also positively predict gambling severity (Krueger et al., 2005; Steel and Blaszczynski, 1998) and short-term engagement with treatment (Leblond et al., 2003) mirroring relationships that have been observed in substance use disorders (Verdejo-Garcia et al., 2008). Two prospective studies have also linked trait impulsivity in adolescence and young adulthood with later development of gambling, as well as substance use problems, at 3 to 4 year follow-up (Slutske et al., 2005; Vitaro et al., 1999).

The neuropsychological profile of pathological gambling tells a more complex story. Robust impairments have also been observed in studies that used the delay-discounting procedure, where participants choose between small rewards available immediately, or larger rewards available at some point in the future. Steeper delay-discounting is reported in pathological gamblers (Dixon et al., 2003; Petry, 2001; Petry and Casarella, 1999b). Petry (2001) also examined the issue of substance misuse co-morbidity, by comparing groups with pathological gambling and substance-use disorders, pathological gambling alone, and controls. Steeper discounting of future rewards was observed in both groups with pathological gambling, but there was an additive effect of substance abuse, with the steepest rate in the group with both gambling and substance abuse problems.

Measures of response inhibition yield a more inconsistent picture, however. Lawrence and colleagues (2009a) investigated action cancellation function using the Stop-Signal procedure. These authors observed deficits in both the stop-signal reaction time (SSRT) and in basic psychomotor speed ("go" reaction times) in the alcohol-dependent participants, but the problem gamblers and healthy controls did not differ on either measure (SSRT means = 185 ms and 184 ms, respectively). While an earlier study did report a significant SSRT deficit in a (more severe) group of treatment-seeking pathological gamblers (Goudriaan et al., 2006), this was not substantiated in a further study in which only gamblers with co-morbid ADHD were impaired (Rodriguez-Jimenez et al., 2006).

Recent work has begun to consider this heterogeneity in pathological gambling more explicitly. Common gambling games differ on a multitude of psychological parameters that are known to influence rates of responding in animal behavior (e.g., delay between gambling response and its outcome), and contrasting motivational influences have also been described in problem gamblers; some gamblers emphasize the hedonic thrill and physiological arousal

induced by gambling, while others describe an alleviation of low mood and distraction from stressors (i.e., negative reinforcement model). Within Blaszczynski and Nower's (2002) influential Pathways Model of pathological gambling, executive dysfunction provides one source of heterogeneity. The model describes a subgroup of pathological gamblers with "antisocial impulsive" tendencies, characterized by premorbid ADHD or antisocial personality disorder (American Psychiatric Association, 1994), coupled with neuropsychological evidence of dysexecutive syndrome. It is likely that assays of action cancellation problems (or response inhibition), such as measured by the Stop-Signal, are aligned with this executive dysfunction.

The preceding discussion highlights a number of commonalities between alcohol and substance use disorders on the one hand and pathological gambling on the other hand in relation to impulsivity-related measures. However, the cognitive perspective on gambling and pathological gambling emphasizes the presence of cognitive distortions that do not have an obvious correlate in the substance use disorders (Ladouceur and Walker, 1996). These distortions occur in the processing of probability, randomness and skill during gambling, and cause gamblers to over-estimate their chances of winning. Two of the more widely studied distortions are the illusion of control, where the gambler infers a degree of skill in a game that is determined by chance alone, and the gambler's fallacy, in which gamblers infer patterns of outcomes in random data, and believe that a win is somehow "due" after a protracted run of losses (Clark, 2009; Ladouceur et al., 1996).

Cognitive biases in *attention* have been clearly demonstrated in substance use disorders, such as the slowed naming of drug-relevant words on an emotional Stroop task, and comparable biases for gambling-relevant words are also observed in problem gamblers (Boyer and Dickerson, 2003; McCusker and Gettings, 1997). However, it is currently unclear whether distortions of probability and reasoning also generalize from pathological gambling to drug addiction. Recent data indicate that these distortions recruit neural circuitry of core relevance to the mechanisms of impulsivity and the clinical phenotype of addiction. For example, Clark and colleagues have used fMRI to study the brain response to gambling *near-misses*; nonwin outcomes that are somehow proximal to actual wins. Gamblers frequently recognize near-miss outcomes and report that they encourage further play, despite the objective fact that in a game of chance (e.g. the lottery), a near-miss provides absolutely no useful information to guide ongoing play. Clark and colleagues (2009) devised a computerized slot-machine task that allowed the comparison of monetary wins, near-misses (where the reel stopped one position from the payline), and "full-misses." Subjective ratings showed that near-misses were experienced as aversive (more unpleasant than full-misses) but increased the desire to continue with the game. In a second group of subjects who played the task during an fMRI scan, near-misses were observed to activate the ventral striatum, insula, medial prefrontal cortex that responded to monetary wins. Neuronal response to near-misses in the insula cortex predicted subjective effects of near-misses to encourage further play, and also predicted individual differences on a questionnaire measure of cognitive distortions (Clark et al., 2009).

Of the neuropsychological impairments that might be shared between pathological gambling and substance users, problems with decision-making appear to be one of the most salient

(Bechara and Damasio, 2002; Bechara et al., 2002; Ersche et al., 2005; Goudriaan et al., 2005; Lawrence et al., 2009a). In a clinical context, heightened impulsivity often appears as a significant contributor to the maladaptive choices that clinical patients sometime make and which, for example, appear to increase the prospects of relapse in alcohol (Bechara et al., 2001) and substance misuse (Adinoff et al., 2007). While some forms of impulsive behavior seem to involve predominantly problems in behavioral control as either action restraint or cancellation (Bjork et al., 2004; Robbins, 2002; Schachar et al., 2001), others involve variability in the capacity to select between actions that vary in their evaluated outcomes (Rushworth et al., 2007; Schweighofer et al., 2007); in this way, increased delay-discounting is as much a manifestation of altered decision-making as faulty impulse control.

There are robust deficits on measures of risky decision-making, including the IGT (Cavedini et al., 2002; Petry, 2001), the Balloon Analogue Risk Task (Lejuez et al., 2003), the Cambridge Gamble Task (Lawrence et al., 2009a), and the Game of Dice task (Brand, 2004). In the Cambridge Gamble Task, participants are presented with an array of 10 red and blue boxes (e.g., 8 red, 2 blue), and must guess whether a token has been hidden under a red or blue box. Following this probability decision, they wager points on its outcome. Lawrence and colleagues (2009a) found that both a sample of problem gamblers and a sample of alcohol dependents made the same probability decisions as control participants (although the alcohol-dependent participants showed longer deliberation times) (Lawrence et al., 2009a). However, both clinical groups placed elevated wagers compared to controls; an effect previously observed in individuals with ventromedial prefrontal lesions (Clark et al., 2008).

Pathological gambling involves one prominent exemplar of impaired decision-making that reflects the psychological addiction of the disorder; namely, the tendency to continue gambling to recover previous losses. This behavior is known as “loss-chasing” (Lesieur, 1984). Loss-chasing is observed in both recreational gamblers (Dickerson et al., 1987) and in pathological gamblers (American Psychiatric Association, 2000). Descriptive theories of choice under uncertainty attribute this behavior to the fact that losses fall on the convex part of a psychophysical function relating monetary value to its subjective value, such that the decrease in utility associated with gambling and incurring further losses is proportionately smaller than the reduction in utility associated with sustaining the losses already incurred (Khaneman and Tversky, 2000). Presumably, the neural (and neurochemical) systems involved in resolving such dilemmas contribute to the loss-chasing observed in both recreational and pathological gamblers.

Loss-chasing is strongly associated with impaired control over gambling behavior (Lesieur, 1979) and has the effect of accelerating gambling involvement, increasing affected individuals’ financial liabilities but, at the same time, diminishing the financial resources available to meet them. Thus, loss-chasing is a significant precipitant of pathological gambling’s adverse familial, social, and occupational consequences (Corless and Dickerson, 1989b). Despite the centrality of loss-chasing to pathological gambling, we know very little about the brain circuits that support it. Identifying its neural substrates might help us to understand how the brain dysfunctions within mesolimbic pathways recently identified in

samples of pathological gamblers can contribute to the disorder's clinical presentation (Potenza et al., 2003; Reuter et al., 2005).

Recently, Campbell-Meiklejohn and colleagues (2008) have developed a laboratory mode of loss-chasing behavior, focusing on what happens when gamblers decide they have to stop gambling. Participants are presented with opportunities to choose between chasing an incurred loss or quitting, avoiding further loss. At the start of the study session, participants are told that they have a fictional £20,000 to play with, but that the participant with highest remaining points at the end of the game will win a real monetary prize. On each "round" of the game, an arbitrary amount of money (£10, £20, £40, £80, or £160) is subtracted from their game total. At this point, participants can choose to "Quit," accepting this loss and ending the round immediately ("chase-quit"), or they can choose to "Play," that is, chase the loss. Thus, they can gamble on recovering the loss but at the risk of incurring a further penalty of doubling their current losses. If the outcome of this gamble is positive ("chase-win"), the loss is recovered and the round ends. If the outcome is negative ("chase-loss"), the loss is doubled and participants are given another chance to quit or chase in the next round of the game. In this way, participants played an enforced "Martingale" system. Campbell-Meiklejohn and colleagues (2008) used fMRI to identify the neural substrates associated with such decisions to chase losses or quit.

Clinical studies indicate loss-chasing is driven by conflicted motivations. On the one hand, there is a wearing anxiety associated with the gambler's already-acquired liabilities, but also the persisting hope that the next gamble will be the one that clears the slate: "It's one crisis after another, and you gamble to get even....one big hit, make that one big hit, and pay off the debts and never gamble again" (Lesieur, 1977).

However, on the other hand, gamblers also report accompanying dysphoria and a prominent sense of dread that yet another bad outcome will result in an even more desperate situation: "Then came the feeling....of uneasiness within myself; a feeling of, probably you might call it of impending doom or disaster, that I had never had before. There was no way that I wasn't going to blow everything" (Lesieur, 1977).

On this basis, Campbell-Meiklejohn and colleagues (2008) hypothesized that decisions to chase losses depend upon activity in neural pathways involved in reward expectancy; while decisions to quit chasing losses depend upon activity in other neural circuits involved in visceral arousal and the anticipation of aversive consequences. Twenty-three participants showed a steady willingness to gamble in an effort to recover losses. On average, they chose to chase the loss on 0.73 ± 0.02 (SE) of all decisions and the mean number of chase decisions per round was 2.07 trials (± 0.07 ; min 1.5, max 2.88). The proportion of decisions to chase on the loss-chasing game was strongly associated with the total score on an independent 14-item assessment of participants' propensity to chase in other gambling activities (Corless and Dickerson, 1989a) ($r = 0.67$, $p < 0.001$).

In imaging terms, deciding to keep chase losses in an attempt to recover previous losses was associated with increased activity in the ventromedial prefrontal cortex (along the gyrus rectus) on the left, with further peaks in the subgenual cingulate cortex bilaterally (area 25).

There is extensive evidence that neural activity in ventromedial prefrontal cortex codes the expectation of reward (Galvan et al., 2005; Knutson et al., 2005). It has also been argued that this activity reflects the representation of reward values for goal-directed actions (Hampton et al., 2006). The subgenual cingulate cortex has also been implicated in the aspects of reward processing, including the representation of strong appetitive states such as hunger (Tataranni et al., 1999), suggesting that this cortical area is also involved in the incentive-motivational aspects of chasing losses. Clinical research indicates that loss-chasing is sustained by the persistent, undeterred belief that winning outcomes are imminent (Ladouceur et al., 1996; Lesieur, 1977). Campbell-Meiklejohn and colleagues (2008)'s fMRI findings provide at least some evidence to support this claim.

By contrast, decisions to quit chasing losses were associated with increased activity in the anterior insula cortex and dorsal anterior cingulate cortex. The activity in the dorsal anterior cingulate cortex included not only anterior cingulate proper (area 24) but also the paracingulate cortex (area 32). Decisions to quit were also associated with substantial signal increases along the middle frontal gyrus, in the posterior cingulate cortex, and the parietal cortex.

There are 2 implications of these results. The first is that when gamblers decide to quit, they do so, anticipating the negative consequences of choices to keep gambling that end up producing larger losses still. Activation in the insula is associated with both negative states such as pain and disgust (Singer et al., 2004; Wicker et al., 2003) and the anticipation of negative outcomes (Critchley et al., 2004; Ploghaus et al., 1999). It has also been suggested that the anterior insula cortex represents the visceral sensations that provide a substrate for the subjective awareness of emotionally potent information (Craig, 2002). Insula activity has also been linked to increased trait harm avoidance while making decisions (Paulus et al., 2003) and observed to precede risk-free choices in the context of a financial investment task (Kuhnen and Knutson, 2005). Activity within the anterior cingulate cortex may also reflect, in part, the anticipation of negative states through its role in the processing of pain information (Ploghaus et al., 1999). Therefore, signal change observed within the dorsal anterior cingulate cortex and the insula cortex when gamblers decide to quit the chase may reflect the sensations, imagery, and emotional arousal associated with anticipating further negative consequences.

The second implication of the activations revealed in the contrast of deciding to quit compared to deciding to chase is that the gamblers may be in especial conflict on choices in which they quit, evidenced by significantly longer deliberation times required to make a decision to stop gambling. Activity in the dorsal anterior cingulate cortex could also reflect the monitoring of conflict. Activity in this area has been reported in situations in which participants monitor cognitive states involving conflict or competition between activated responses (Carter et al., 1998; Kerns et al., 2004); and may additionally represent both the positive and negative value of candidate actions (Bush et al., 2002). Activity along the medial superior frontal gyrus has also been reported in situations in which experimental participants have to switch between actions sets (Rushworth et al., 2004).

As noted previously, activity was increased in the posterior cingulate cortex and parietal cortex when participants decided to quit the chase compared to when they decided to gamble, and also when they successfully cleared their losses. Neuronal activity within these areas is sensitive to the uncertainty of rewards linked to candidate actions (McCoy and Platt, 2005); and to be involved in integrating uncertainty and reward information to determine action value (Platt and Glimcher, 1999). Therefore, these results indicate that both decisions to quit—producing immediate losses—and successfully clearing losses (having decided to chase) engage a distributed network of neural systems that are implicated in monitoring processing conflicts, instrumental learning, risk appraisal and value attached to individual choices, and the subjective experience of emotional arousal.

On the basis of these data, Campbell-Meiklejohn and colleagues (2008) suggest that decision to chase or quit depends on a balance of activity in dissociable neural networks associated with the competing motivations of reward expectancy and anticipated aversive consequences.

To study this balance further, activity when chasing or quitting was compared with a third control condition where no decision was made before a response. Decisions to quit were associated with distinctive pattern of signal change such that activity within the left anterior insula, dorsal anterior cingulate cortex, posterior cingulate, and parietal cortices was increased relative to the control condition, while activity within the ventromedial prefrontal and subgenual cingulate cortices that had been active during decision to chase was significantly reduced. Complementing this dissociation, decisions to chase also involved reduced activity in right anterior insula, dorsal anterior cingulate cortex, and the inferior frontal gyrus relative to the control condition (Campbell-Meiklejohn et al., 2008).

Reduced activity within the ventromedial prefrontal cortex during decisions to quit supports the hypothesis that chasing involves rebalanced activity within systems supporting reward expectancy. However, these data also indicate that the reductions in signal observed within the subgenual cingulate cortex when participants decided to quit reflects the influence of negative affect on loss-chasing behavior. Reductions in % signal within the subgenual cingulate cortex during decisions to quit were associated with higher scores on a psychometric measure of state negative affect that captures elements of dysphoria ($r = 0.424$, $p < 0.05$). Activity within this area is important in the sadness and anxiety (Drevets, 2000). Problem gambling is exacerbated by mood disorders including depressive illness (Corless and Dickerson, 1989b); thus, the subgenual cingulate cortex activity may be the neural locus for this effect.

Pathological gambling is often associated with a number of exaggerated cognitive and behavioral biases that seem relevant to the maintenance of the disorder; however, the experimental investigation into the neural systems that support these biases has only just begun. The data reported by Campbell-Meiklejohn and colleagues (2008) and Clark and colleagues (2009) suggest that it may be possible to specify more precisely the neural machinery that supports cognitive biases in gambling behavior, with the prospect of using such models to understand how dysfunction within mesolimbic circuits and other neuromodulators confers vulnerability to develop problem gambling behavior.

GENERAL DISCUSSION

The evidence reviewed previously indicates that impulsivity can also be a severity marker for psychological disorders associated with, and comorbid for, alcohol use. Thus, there are associations between high-trait impulsivity and earlier onset of illness, more depressive episodes and increased suicidality in individuals with the diagnoses of bipolar disorder (Swann et al., 2009a). Impulsivity also goes along with the incidence of relapsing illness in substance users (Verdejo-Garcia et al., 2008), pathological gamblers (Blanco et al., 2009) and patients with bipolar disorder indicated, in the latter case, by findings that scores on the psychometric assessments (BIS-11) and impairments in laboratory measures of impulsivity are correlated with the frequency of illness (Swann et al., 2009a).

At the current time, it is unclear whether these different forms of impulsivity constitute a set of predisposing traits that increase the probability of developing clinically significant illness, or instead represent the cumulative effects of previous illness episodes; in the case of substance use, it may be that the cumulative effects of alcohol and drug use promote the expression impulsive behavior. Experiments with animal models are needed to test between these possibilities. However, at least in the case of stimulants, reduced D₂ receptor expression promotes impulsive behavior and drug self-administration (Dalley et al., 2007a) while drug administration seems to have *both* short and long-term effects on subsequent cognitive (attentional) function (Dalley et al., 2007b). Consistent with the possibility that heightened impulsiveness might be a predisposing trait (or set of traits), Saunders and colleagues (2008) report that first-degree relatives of individuals with alcoholism showed lower socialization scores than individuals with no such familial risk, alongside an increased number of commission errors during performance of a go/no-go reaction time task (Saunders et al., 2008). Other data suggest that such impairments might also be differentially susceptible to the reduced serotonin activity (LeMarquand et al., 1999) Finally, first degree of individuals with bipolar disorder show evidence of weakened response inhibition as part of a larger cognitive endophenotype (Bora et al., 2009).

It is also unclear whether particular impairments (e.g., failing response inhibition) have a broadly similar impact on different disorders or whether particular impairments play a more pivotal role in the development of some aspects of psychopathology compared to others (e.g., intolerance of longer delays to larger rewards in substance use compared to bipolar disorder). Holmes and colleagues report that prior history of alcohol abuse exacerbates the impulsive behavior and risk decision-making shown by patients with bipolar disorder (Holmes et al., 2009). The data presented here suggest that these patient populations tend to share fairly generalized impairments across the several measures of impulsivity tested; however, improvements in the design and sensitivity of experimental models of impulsivity may yet reveal evidence for greater specificity between disorders.

The cognitive impairments described in the investigations reviewed here also make contact with what we know about the mechanisms of impulsivity as revealed by experiments with animal and human subjects (Dalley et al., 2008; Jentsch and Taylor, 1999). These include the control of prematurely activated response repertoires (as tested by continuous performance paradigms (Bjork et al., 2004; Finn et al., 2002; Robbins, 2002); choices

between small immediate rewards and larger delayed reward (as tested by delay-discounting tasks) (Bjork et al., 2004; Winstanley et al., 2006a,c), as well as the gathering of adequate information before action initiation (as tested in tasks of reflection impulsivity) (Clark et al., 2006; Evenden, 1999a). Thus, findings that deficient response inhibition and risky choice in substance users are associated with altered signaling within the dorsal anterior cingulate cortex and its dorsomedial surround are consistent with observation that lesions of dorsomedial-striatal circuitry can also increase impulsive behaviors in rats (Muir et al., 1996; Rogers et al., 2001), and with evidence that the dorsal anterior cingulate cortex is involved in value-based choices in healthy adult volunteers (Rogers et al., 2004; Rushworth et al., 2004).

Similarly, findings that yohimbine impairs response inhibition (Swann et al., 2005a) are convergent with the results of pharmacological challenges in rats, demonstrating improvements in action cancellation following atomoxetine (Robinson et al., 2008). They are also consistent with the hypothesis that a sensitized response to catecholamine activity promotes impulsivity in mania (Swann et al., 2003, 2005a). There has been relatively little research into the relationship between impulsivity as a trait and its impact upon behavioral control under different kinds of emotional states (Benazzi, 2007). However, phasic noradrenaline activity within the dorsal anterior cingulate cortex may influence the control of responses as a function of the perceived reward value of an activity (Aston-Jones and Cohen, 2005). It is possible that heightened mood in the manic state might disrupt behavioral control through this system (Swann et al., 2005b).

As outlined previously, pathological gambling exhibits behaviors that bear comparison to those associated with substance-use disorders including alcoholism. These disorders involve the persistence of motivated behaviors—gambling and drug use—in the face of their considerable, but readily apparent, adverse health-related, occupational, and social consequences. In terms of more clearly defined diagnostic criteria, pathological gamblers can experience symptoms of withdrawal, tolerance and cravings apparently comparable to those experienced by individuals with substance dependence disorders (Shaffer et al., 2004). Consistent with this, problem gambling is associated with some, but not all, of the neuropsychological impairments observed in alcoholic-dependent individuals (Lawrence et al., 2009a). Several of these seem to reflect impulsivity phenotypes, including an inability to maintain action restraint (“go-no go” performance), deficient capacity to tolerate delays to larger rewards and problems in risky decision-making. Collectively, the above observations have increased the prospects that pathological gambling will be included alongside the substance use disorders within the formulation of DSM-V (O’Brien, Addiction vs. Dependence for DSM V, College of Problems of Drug Dependence 71st Annual Scientific Meeting, Reno, June 22nd 2009).

While it is true that we learn a lot about psychological illnesses by studying how they are the same, we can also, perhaps, learn more by testing how they might be different. One possible example of this is the tendency for almost-winning (or near-misses) to promote further play in pathological gamblers (Clark et al., 2009). Loss-chasing may be another. Patients with bipolar disorder, substance users, alcoholic individuals and pathological gamblers all exhibit impairments in decision-making, and these impairments can predict relapse in both

substance users (Green et al., 2009b) and pathological gamblers (Blanco et al., 2009). However, the kinds of decisions that these clinical populations find challenging may differ. In the case of pathological gambling, the most obvious faulty choices involve decisions to keep gambling to recover previous losses, as “loss-chasing.”

Loss-chasing poses a challenge to our understanding of the other impulsive disorders discussed previously. At first glance, loss-chasing seems to be a behavior that is highly specific to gambling and pathological gamblers. It is behavior that is *not* obviously impulsive; it is aversively motivated by the strong desire to avoid a known bad outcome. In this sense, loss-chasing can be seen as an “escape” behavior. Decisions to chase set the relative value of a known bad outcome against the value of a larger but uncertain bad outcome. However, where significant financial liabilities have already accumulated, loss-chasing can also reflect decisions “against one’s best interests and inability to learn from previous mistakes, with repeated decisions leading to negative consequences” (Bechara and Damasio, 2005). Substance use, and alcoholism (but less obviously, bipolar disorder), seem also to show the persistence of behaviors that impose higher and higher costs, at each point testing whether the affected individual is able to stop. Therefore, it is possible that individuals with alcohol and substance-use problems will also show deficits on the laboratory model of loss-chasing behavior, suggesting that their shared mechanisms go beyond impulse control and reflect the evaluation of present against future bad outcomes.

REFERENCES

- Adinoff B, Rilling LM, Williams MJ, Schreffler E, Schepis TS, Rosvall T, Rao U. Impulsivity, neural deficits, and the addictions: the “oops” factor in relapse. *J Addict Dis.* 2007; 26(Suppl 1):25–39. [PubMed: 19283972]
- Allen TJ, Moeller FG, Rhoades HM, Cherek DR. Impulsivity and history of drug dependence. *Drug Alcohol Depend.* 1998; 50:137–145. [PubMed: 9649965]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed.. American Psychiatric Association; Washington, DC.: 1994.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed.. American Psychiatric Publishing Inc.; Washington, DC.: 2000. Text Revision
- Arnsten AF, Mathew R, Ubriani R, Taylor JR, Li BM. Alpha-1 noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. *Biol Psychiatry.* 1999; 45:26–31. [PubMed: 9894572]
- Aron AR. The neural basis of inhibition in cognitive control. *Neuroscientist.* 2007; 13:214–228. [PubMed: 17519365]
- Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci.* 2005; 28:403–450. [PubMed: 16022602]
- Bari A, Eagle DM, Mar AC, Robinson ES, Robbins TW. Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. *Psychopharmacology (Berl).* 2009; 205:273–283. [PubMed: 19404616]
- Barratt ES. Factor analysis of some psychometric measures of impulsivity and anxiety. *Psychol Rep.* 1965; 16:547–554. [PubMed: 14285869]
- Barratt, E. Impulsivity: integrating cognitive, behavioral, biological, and environmental data. In: McCown, WG.; Johnson, JL.; Shure, MB., editors. *The Impulsive Client: Theory, Research, and Treatment.* American Psychological Association; Washington, DC: 1993.
- Baunez C, Robbins TW. Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. *Eur J Neurosci.* 1997; 9:2086–2099. [PubMed: 9421169]

- Bechara A, Damasio H. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia*. 2002; 40:1675–1689. [PubMed: 11992656]
- Bechara A, Damasio AR. The somatic marker hypothesis: a neural theory of economic decision. *Games Econ Behav*. 2005; 52:336–372.
- Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*. 1994; 50:7–15. [PubMed: 8039375]
- Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*. 2001; 39:376–389. [PubMed: 11164876]
- Bechara A, Dolan S, Hindes A. Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? *Neuropsychologia*. 2002; 40:1690–1705. [PubMed: 11992657]
- Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*. 2000; 123(Pt 11):2189–2202. [PubMed: 11050020]
- Benazzi F. Impulsivity in bipolar-II disorder: trait, state, or both? *Eur Psychiatry*. 2007; 22:472–478. [PubMed: 17517499]
- Bickel WK, Marsch LA. Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction*. 2001; 96:73–86. [PubMed: 11177521]
- Bickel WK, Odum AL, Madden GJ. Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology*. 1999; 146:447–454. [PubMed: 10550495]
- Bjork JM, Hommer DW, Grant SJ, Danube C. Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1-/type 2-like traits. *Alcohol*. 2004; 34:133–150. [PubMed: 15902907]
- Bjork JM, Momenan R, Smith AR, Hommer DW. Reduced posterior mesofrontal cortex activation by risky rewards in substance-dependent patients. *Drug Alcohol Depend*. 2008; 95:115–128. [PubMed: 18295984]
- Blanco C, Potenza MN, Kim SW, Ibanez A, Zaninelli R, Saiz-Ruiz J, Grant JE. A pilot study of impulsivity and compulsivity in pathological gambling. *Psychiatry Res*. 2009; 167:161–168. [PubMed: 19339053]
- Blaszczynski A. Pathological gambling and obsessive-compulsive spectrum disorders. *Psychol Rep*. 1999; 84:107–113. [PubMed: 10203933]
- Blaszczynski A, Nower L. A pathways model of problem and pathological gambling. *Addiction*. 2002; 97:487–499. [PubMed: 12033650]
- Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord*. 2009; 113:1–20. [PubMed: 18684514]
- Boyer M, Dickerson M. Attentional bias and addictive behaviour: automaticity in a gambling-specific modified Stroop task. *Addiction*. 2003; 98:61–70. [PubMed: 12492756]
- Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR. Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc Natl Acad Sci USA*. 2002; 99:523–528. [PubMed: 11756669]
- Campbell-Meiklejohn DK, Woolrich MW, Passingham RE, Rogers RD. Knowing when to stop: the brain mechanisms of chasing losses. *Biol Psychiatry*. 2008; 63:293–300. [PubMed: 17662257]
- Cardinal RN. Neural systems implicated in delayed and probabilistic reinforcement. *Neural Netw*. 2006; 19:1277–1301. [PubMed: 16938431]
- Cardinal RN, Winstanley CA, Robbins TW, Everitt BJ. Limbic corticostriatal systems and delayed reinforcement. *Ann N Y Acad Sci*. 2004; 1021:33–50. [PubMed: 15251872]
- Carroll KM, Rounsaville BJ, Bryant KJ. Alcoholism in treatment-seeking cocaine abusers: clinical and prognostic significance. *J Stud Alcohol*. 1993; 54:199–208. [PubMed: 8459714]
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*. 1998; 280:747–749. [PubMed: 9563953]

- Castellani B, Rugle L. A comparison of pathological gamblers to alcoholics and cocaine misusers on impulsivity, sensation seeking, and craving. *Int J Addict*. 1995; 30:275–289. [PubMed: 7790128]
- Cavedini P, Riboldia G, Kellera R, D'Annunzio A, Bellodi L. Frontal lobe dysfunction in pathological gambling patients. *Biol Psychiatry*. 2002; 51:334–341. [PubMed: 11958785]
- Chamberlain SR, Del Campo N, Dowson J, Muller U, Clark L, Robbins TW, Sahakian BJ. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. *Biol Psychiatry*. 2007; 62:977–984. [PubMed: 17644072]
- Chamberlain SR, Hampshire A, Muller U, Rubia K, Del Campo N, Craig K, Renner T, Suckling J, Roiser JP, Grant JE, Bullmore ET, Robbins TW, Sahakian BJ. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. *Biol Psychiatry*. 2009; 65:550–555. [PubMed: 19026407]
- Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science*. 2006; 311:861–863. [PubMed: 16469930]
- Chen AC, Porjesz B, Rangaswamy M, Kamarajan C, Tang Y, Jones KA, Chorlian DB, Stimus AT, Begleiter H. Reduced frontal lobe activity in subjects with high impulsivity and alcoholism. *Alcohol Clin Exp Res*. 2007; 31:156–165. [PubMed: 17207114]
- Chudasama Y, Passetti F, Rhodes SE, Lopian D, Desai A, Robbins TW. Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. *Behav Brain Res*. 2003; 146:105–119. [PubMed: 14643464]
- Clark L. Decision-making during gambling: an integration of cognitive and psychobiological approaches. *Philos Trans R Soc Lond B Biol Sci*. 2009; 365:319–330. [PubMed: 20026469]
- Clark L, Bechara A, Damasio H, Aitken MR, Sahakian BJ, Robbins TW. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain*. 2008; 131(Pt 5):1311–1322. [PubMed: 18390562]
- Clark L, Cools R, Robbins TW. The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. *Brain Cogn*. 2004; 55:41–53. [PubMed: 15134842]
- Clark L, Iversen SD, Goodwin GM. Sustained attention deficit in bipolar disorder. *Br J Psychiatry*. 2002; 180:313–319. [PubMed: 11925353]
- Clark L, Lawrence AJ, Astley-Jones F, Gray N. Gambling near-misses enhance motivation to gamble and recruit win-related brain circuitry. *Neuron*. 2009; 61:481–490. [PubMed: 19217383]
- Clark L, Robbins TW, Ersche KD, Sahakian BJ. Reflection impulsivity in current and former substance users. *Biol Psychiatry*. 2006; 60:515–522. [PubMed: 16448627]
- Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry*. 1987; 44:573–588. [PubMed: 3579504]
- Corless T, Dickerson M. Gamblers' self-perceptions of the determinants of impaired control. *Br J Addict*. 1989a; 84:1527–1537. [PubMed: 2611437]
- Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002; 3:655–666. [PubMed: 12154366]
- Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neurosci*. 2004; 7:189–195. [PubMed: 14730305]
- Cunningham-Williams RM, Gruzza RA, Cottler LB, Womack SB, Books SJ, Przybeck TR, Spitznagel EL, Cloninger CR. Prevalence and predictors of pathological gambling: results from the St. Louis personality, health and lifestyle (SLPHL) study. *J Psychiatr Res*. 2005; 39:377–390. [PubMed: 15804388]
- Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K, Pena Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science*. 2007a; 315:1267–1270. [PubMed: 17332411]
- Dalley JW, Laane K, Theobald DE, Pena Y, Bruce CC, Huszar AC, Wojcieszek M, Everitt BJ, Robbins TW. Enduring deficits in sustained visual attention during withdrawal of intravenous methylene-dioxymethamphetamine self-administration in rats: results from a comparative study

- with d-amphetamine and methamphetamine. *Neuropsychopharmacology*. 2007b; 32:1195–1206. [PubMed: 17035931]
- Dalley JW, Mar AC, Economidou D, Robbins TW. Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. *Pharmacol Biochem Behav*. 2008; 90:250–260. [PubMed: 18272211]
- Dickerson M, Hinchy J, Fabre J. Chasing, arousal and sensation seeking in off-course gamblers. *Br J Addict*. 1987; 82:673–680. [PubMed: 3475105]
- Dickman, S. Impulsivity and information processing. In: McCown, WG.; Johnson, JL.; Shure, MB., editors. *The Impulsive Client: Theory, Research, and Treatment*. American Psychological Association; Washington, DC: 1993.
- Dienes KA, Hammen C, Henry RM, Cohen AN, Daley SE. The stress sensitization hypothesis: understanding the course of bipolar disorder. *J Affect Disord*. 2006; 95:43–49. [PubMed: 16837055]
- Dixon MR, Marley J, Jacobs EA. Delay discounting by pathological gamblers. *J Appl Behav Anal*. 2003; 36:449–458. [PubMed: 14768665]
- Dom G, De Wilde B, Hulstijn W, van den Brink W, Sabbe B. Behavioural aspects of impulsivity in alcoholics with and without a cluster-B personality disorder. *Alcohol Alcohol*. 2006; 41:412–420. [PubMed: 16782972]
- Drevets WC. Neuroimaging studies of mood disorders. *Biol Psychiatry*. 2000; 48:813–829. [PubMed: 11063977]
- Drouin C, Blanc G, Villegier AS, Glowinski J, Tassin JP. Critical role of alpha1-adrenergic receptors in acute and sensitized locomotor effects of D-amphetamine, cocaine, and GBR 12783: influence of preexposure conditions and pharmacological characteristics. *Synapse*. 2002; 43:51–61. [PubMed: 11746733]
- Eagle DM, Bari A, Robbins TW. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology (Berl)*. 2008; 199:439–456. [PubMed: 18542931]
- Easton CJ, Sacco KA, Neavins TM, Wupperman P, George TP. Neurocognitive performance among alcohol dependent men with and without physical violence toward their partners: a preliminary report. *Am J Drug Alcohol Abuse*. 2008; 34:29–37. [PubMed: 18161641]
- Economidou D, Pelloux Y, Robbins TW, Dalley JW, Everitt BJ. High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. *Biol Psychiatry*. 2009; 65:851–856. [PubMed: 19181308]
- Ersche KD, Fletcher PC, Lewis SJ, Clark L, Stocks-Gee G, London M, Deakin JB, Robbins TW, Sahakian BJ. Abnormal frontal activations related to decision-making in current and former amphetamine and opiate dependent individuals. *Psychopharmacology (Berl)*. 2005; 180:612–623. [PubMed: 16163533]
- Evenden JL. The pharmacology of impulsive behaviour in rats II: the effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and other drugs on fixed consecutive number schedules (FCN 8 and FCN 32). *Psychopharmacology*. 1998a; 138:283–294. [PubMed: 9725750]
- Evenden JL. The pharmacology of impulsive behaviour in rats IV: the effects of selective serotonergic agents on a paced fixed consecutive number schedule. *Psychopharmacology*. 1998b; 140:319–330. [PubMed: 9877012]
- Evenden JL. The pharmacology of impulsive behaviour in rats VII: the effects of serotonergic agonists and antagonists on responding under a discrimination task using unreliable visual stimuli. *Psychopharmacology*. 1999a; 146:422–431. [PubMed: 10550492]
- Evenden JL. Varieties of impulsivity. *Psychopharmacology*. 1999b; 146:348–361. [PubMed: 10550486]
- Finn PR, Mazas CA, Justus AN, Steinmetz J. Early-onset alcoholism with conduct disorder: go/no go learning deficits, working memory capacity, and personality. *Alcohol Clin Exp Res*. 2002; 26:186–206. [PubMed: 11964558]
- Frost RO, Meagher BM, Riskind JH. Obsessive-compulsive features in pathological lottery and scratch-ticket gamblers. *J Gambl Stud*. 2001; 17:5–19. [PubMed: 11705017]

- Galvan A, Hare TA, Davidson M, Spicer J, Glover G, Casey BJ. The role of ventral frontostriatal circuitry in reward-based learning in humans. *J Neurosci*. 2005; 25:8650–8656. [PubMed: 16177032]
- Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *Am J Psychiatry*. 2007a; 164:43–51. [PubMed: 17202543]
- Goldstein RZ, Tomasi D, Alia-Klein N, Cottone LA, Zhang L, Telang F, Volkow ND. Subjective sensitivity to monetary gradients is associated with frontolimbic activation to reward in cocaine abusers. *Drug Alcohol Depend*. 2007b; 87:233–240. [PubMed: 16997508]
- Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W. Decision making in pathological gambling: a comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. *Brain Res Cogn Brain Res*. 2005; 23:137–151. [PubMed: 15795140]
- Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W. Neurocognitive functions in pathological gambling: a comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction*. 2006; 101:534–547. [PubMed: 16548933]
- Green CE, Moeller FG, Schmitz JM, Lucke JF, Lane SD, Swann AC, Lasky RE, Carbonari JP. Evaluation of heterogeneity in pharmacotherapy trials for drug dependence: a Bayesian approach. *Am J Drug Alcohol Abuse*. 2009a; 35:95–102. [PubMed: 19322730]
- Green CE, Moeller FG, Schmitz JM, Lucke JF, Lane SD, Swann AC, Lasky RE, Carbonari JP, Tyson JE. Evaluation of heterogeneity in pharmacotherapy trials for drug dependence: a Bayesian approach. *Am J Drug Alcohol Abuse*. 2009b; 35:7.
- Hampton AN, Bossaerts P, O'Doherty JP. The role of the ventromedial prefrontal cortex in abstract state-based inference during decision making in humans. *J Neurosci*. 2006; 26:8360–8367. [PubMed: 16899731]
- Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. *J Neurosci*. 2004; 24:11017–11022. [PubMed: 15590917]
- Hinslie, L.; Shatzky, J. *Psychiatric Dictionary*. Oxford University Press; New York: 1940.
- Holmes KM, Bearden CE, Barguil M, Fonseca M, Serap Monkul E, Nery FG, Soares JC, Mintz J, Glahn DC. Conceptualizing impulsivity and risk taking in bipolar disorder: importance of history of alcohol abuse. *Bipolar Disord*. 2009; 11:33–40. [PubMed: 19133964]
- Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology*. 1999; 146:373–390. [PubMed: 10550488]
- Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci*. 2003; 23:7839–7843. [PubMed: 12944513]
- Kerns JG, Cohen JD, MacDonald AW 3rd, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. *Science*. 2004; 303:1023–1026. [PubMed: 14963333]
- Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB, Walters EE. The World Health Organization Adult ADHD Self-Report Scale (ASRS). *Psych Med*. 2005; 35:245–256.
- Khaneman, D.; Tversky, A. *Choices Values and Frames*. Cambridge University Press; Cambridge, UK: 2000.
- Kim SW, Grant JE. Personality dimensions in pathological gambling disorder and obsessive-compulsive disorder. *Psychiatry Res*. 2001; 104:205–212. [PubMed: 11728609]
- Knutson B, Taylor J, Kaufman M, Peterson R, Glover G. Distributed neural representation of expected value. *J Neurosci*. 2005; 25:4806–4812. [PubMed: 15888656]
- Krueger TH, Schedlowski M, Meyer G. Cortisol and heart rate measures during casino gambling in relation to impulsivity. *Neuropsychobiology*. 2005; 52:206–211. [PubMed: 16244502]
- Kuhnen CM, Knutson B. The neural basis of financial risk taking. *Neuron*. 2005; 47:763–770. [PubMed: 16129404]

- Kuo PH, Aggen SH, Prescott CA, Kendler KS, Neale MC. Using a factor mixture modeling approach in alcohol dependence in a general population sample. *Drug Alcohol Depend.* 2008; 98:105–114. [PubMed: 18586414]
- Ladouceur R, Paquet C, Dube D. Erroneous perceptions in generating sequences of random events. *J Appl Soc Psychol.* 1996; 26:2157–2166.
- Ladouceur, R.; Walker, M. A cognitive perspective on gambling. In: Salkovskis, PM., editor. *Trends in Cognitive and Behavioral Therapies.* Wiley; New York: 1996.
- Lane SD, Moeller FG, Steinberg JL, Buzby M, Kosten TR. Performance of cocaine dependent individuals and controls on a response inhibition task with varying levels of difficulty. *Am J Drug Alcohol Abuse.* 2007; 33:717–726. [PubMed: 17891664]
- Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L. Problem gamblers share deficits in impulsive decision-making with alcohol-dependent individuals. *Addiction.* 2009a; 104:1006–1015. [PubMed: 19466924]
- Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L. Impulsivity and response inhibition in alcohol dependence and problem gambling. *Psychopharmacology (Berl).* 2009b; 207:163–172. [PubMed: 19727677]
- Leblond J, Ladouceur R, Blaszczynski A. Which pathological gamblers will complete treatment? *Br J Clin Psychol.* 2003; 42(Pt 2):205–209. [PubMed: 12828808]
- Lejuez CW, Aklin WM, Jones HA, Richards JB, Strong DR, Kahler CW, Read JP. The Balloon Analogue Risk Task (BART) differentiates smokers and nonsmokers. *Exp Clin Psychopharmacol.* 2003; 11:26–33. [PubMed: 12622341]
- LeMarquand DG, Benkelfat C, Pihl RO, Palmour RM, Young SN. Behavioral disinhibition induced by tryptophan depletion in nonalcoholic young men with multigenerational family histories of paternal alcoholism. *Am J Psychiatry.* 1999; 156:1771–1779. [PubMed: 10553742]
- Lesieur, H. *The Chase: Career of the Compulsive Gambler.* 1st ed.. Anchor Press/Doubleday; Garden City, NY: 1977.
- Lesieur HR. The compulsive gambler's spiral of options and involvement. *Psychiatry.* 1979; 42:79–87. [PubMed: 760136]
- Lesieur, HR. *The Chase: Career of the Compulsive Gambler.* Schenkman; Cambridge, MA: 1984.
- Lim KO, Choi SJ, Pomara N, Wolkin A, Rotrosen JP. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. *Biol Psychiatry.* 2002; 51:890–895. [PubMed: 12022962]
- Lim KO, Wozniak JR, Mueller BA, Franc DT, Specker SM, Rodriguez CP, Silverman AB, Rotrosen JP. Brain macrostructural and microstructural abnormalities in cocaine dependence. *Drug Alcohol Depend.* 2008; 92:164–172. [PubMed: 17904770]
- Ma L, Hasan KM, Steinberg JL, Narayana PA, Lane SD, Zuniga EA, Kramer LA, Moeller FG. Diffusion tensor imaging in cocaine dependence: regional effects of cocaine on corpus callosum and effect of cocaine administration route. *Drug Alcohol Depend.* 2009; 104:262–267. [PubMed: 19595517]
- McCormick RA, Taber J, Kruegelbach N, Russo A. Personality profiles of hospitalized pathological gamblers: the California Personality Inventory. *J Clin Psychol.* 1987; 43:521–527. [PubMed: 3667946]
- McCoy AN, Platt ML. Risk-sensitive neurons in macaque posterior cingulate cortex. *Nat Neurosci.* 2005; 8:1220–1227. [PubMed: 16116449]
- McCusker CG, Gettings B. Automaticity of cognitive biases in addictive behaviours: further evidence with gamblers. *Br J Clin Psychol.* 1997; 36(Pt 4):543–554. [PubMed: 9403145]
- McElroy SL, Pope HG Jr, Keck PE Jr, Hudson JI, Phillips KA, Strakowski SM. Are impulse-control disorders related to bipolar disorder? *Compr Psychiatry.* 1996; 37:229–240. [PubMed: 8826686]
- McIntyre RS, Keck PE Jr. Comorbidity in bipolar disorder: clinical and research opportunities. *Bipolar Disord.* 2006; 8:645–647. [PubMed: 17156151]
- Miller L. Predicting relapse and recovery in alcoholism and addiction: neuropsychology, personality, and cognitive style. *J Subst Abuse Treat.* 1991; 8:277–291. [PubMed: 1664867]
- Mitchell JM, Fields HL, D'Esposito M, Boettiger CA. Impulsive responding in alcoholics. *Alcohol Clin Exp Res.* 2005; 29:2158–2169. [PubMed: 16385186]

- Mobini S, Body S, Ho MY, Bradshaw CM, Szabadi E, Deakin JF, Anderson IM. Effects of lesions of the orbitofrontal cortex on sensitivity to delayed and probabilistic reinforcement. *Psychopharmacology (Berl)*. 2002; 160:290–298. [PubMed: 11889498]
- Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. *Am J Psychiatry*. 2001a; 158:1783–1793. [PubMed: 11691682]
- Moeller FG, Barratt ES, Fischer CJ, Dougherty DM, Reilly EL, Mathias CW, Swann AC. P300 event-related potential amplitude and impulsivity in cocaine-dependent subjects. *Neuropsychobiology*. 2004; 50:167–173. [PubMed: 15292673]
- Moeller FG, Dougherty DM, Barratt ES, Oderinde V, Mathias CW, Harper RA, Swann AC. Increased impulsivity in cocaine dependent subjects independent of antisocial personality disorder and aggression. *Drug Alcohol Depend*. 2002; 68:105–111. [PubMed: 12167556]
- Moeller FG, Dougherty DM, Barratt ES, Schmitz JM, Swann AC, Grabowski J. The impact of impulsivity on cocaine use and retention in treatment. *J Subst Abuse Treat*. 2001b; 21:193–198. [PubMed: 11777668]
- Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Dougherty DM, Santos RM, Valdes I, Swann AC, Barratt ES, Narayana PA. Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. *Neuropsychopharmacology*. 2005; 30:610–617. [PubMed: 15637640]
- Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Valdes I, Lai LY, Swann AC, Narayana PA. Diffusion tensor imaging eigenvalues: preliminary evidence for altered myelin in cocaine dependence. *Psychiatry Res*. 2007; 154:253–258. [PubMed: 17321725]
- Muir JL, Everitt BJ, Robbins TW. The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. *Cereb Cortex*. 1996; 6:470–481. [PubMed: 8670672]
- Narayana PA, Ahobila-Vajjula P, Ramu J, Herrera J, Steinberg JL, Moeller FG. Diffusion tensor imaging of cocaine-treated rodents. *Psychiatry Res*. 2009; 171:242–251. [PubMed: 19217266]
- Navarra R, Graf R, Huang Y, Logue S, Comery T, Hughes Z, Day M. Effects of atomoxetine and methylphenidate on attention and impulsivity in the 5-choice serial reaction time test. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32:34–41. [PubMed: 17714843]
- Noel X, Van der Linden M, d'Acremont M, Bechara A, Dan B, Hanak C, Verbanck P. Alcohol cues increase cognitive impulsivity in individuals with alcoholism. *Psychopharmacology (Berl)*. 2007; 192:291–298. [PubMed: 17279375]
- O'Brien CP, Volkow N, Li TK. What's in a word? Addiction versus dependence in DSM-V. *Am J Psychiatry*. 2006; 163:764–765. [PubMed: 16648309]
- Overtoom CC, Verbaten MN, Kemner C, Kenemans JL, van Engeland H, Buitelaar JK, van der Molen MW, van der Gugten J, Westenberg H, Maes RA, Koelega HS. Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with attention deficit hyperactivity disorder. *Behav Brain Res*. 2003; 145:7–15. [PubMed: 14529800]
- Patkar AA, Murray HW, Mannelli P, Gottheil E, Weinstein SP, Vergare MJ. Pre-treatment measures of impulsivity, aggression and sensation seeking are associated with treatment outcome for African-American cocaine-dependent patients. *J Addict Dis*. 2004; 23:109–122. [PubMed: 15132346]
- Pattij T, Vanderschuren LJ. The neuropharmacology of impulsive behaviour. *Trends Pharmacol Sci*. 2008; 29:192–199. [PubMed: 18304658]
- Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol*. 1995; 51:768–774. [PubMed: 8778124]
- Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage*. 2003; 19:1439–1448. [PubMed: 12948701]
- Petry NM. Pathological gamblers, with and without substance use disorders, discount delayed rewards at high rates. *J Abnorm Psychol*. 2001; 110:482–487. [PubMed: 11502091]
- Petry NM, Casarella T. Excessive discounting of delayed rewards in substance abusers with gambling problems. *Drug Alcohol Depend*. 1999a; 56:25–32. [PubMed: 10462089]

- van der Plas EA, Crone EA, van den Wildenberg WP, Tranel D, Bechara A. Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women. *J Clin Exp Neuropsychol*. 2008; 31:706–719. [PubMed: 19037812]
- Platt ML, Glimcher PW. Neural correlates of decision variables in parietal cortex. *Nature*. 1999; 400:233–238. [PubMed: 10421364]
- Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN. Dissociating pain from its anticipation in the human brain. *Science*. 1999; 284:1979–1981. [PubMed: 10373114]
- Potenza MN. Should addictive disorders include non-substance-related conditions? *Addiction*. 2006; 101(Suppl 1):142–151. [PubMed: 16930171]
- Potenza MN, Steinberg MA, Skudlarski P, Fulbright RK, Lacadie CM, Wilber MK, Rounsaville BJ, Gore JC, Wexler BE. Gambling urges in pathological gambling: a functional magnetic resonance imaging study. *Arch Gen Psychiatry*. 2003; 60:828–836. [PubMed: 12912766]
- Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat Neurosci*. 2005; 8:147–148. [PubMed: 15643429]
- Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. *Psychopharmacology (Berl)*. 2002; 163:362–380. [PubMed: 12373437]
- Robinson ES, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, Dalley JW, Robbins TW. Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. *Neuropsychopharmacology*. 2008; 33:1028–1037. [PubMed: 17637611]
- Rodriguez-Jimenez R, Avila C, Jimenez-Arriero MA, Ponce G, Monasor R, Jimenez M, Aragues M, Hoenicka J, Rubio G, Palomo T. Impulsivity and sustained attention in pathological gamblers: influence of childhood ADHD history. *J Gambl Stud*. 2006; 22:451–461. [PubMed: 16912931]
- Rogers RD, Baunez C, Everitt BJ, Robbins TW. Lesions of the medial and lateral striatum in the rat produce differential deficits in attentional performance. *Behav Neurosci*. 2001; 115:799–811. [PubMed: 11508719]
- Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, Smith SM. Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. *Biol Psychiatry*. 2004; 55:594–602. [PubMed: 15013828]
- Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, Taylor E. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage*. 2001; 13:250–261. [PubMed: 11162266]
- Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage*. 2003; 20:351–358. [PubMed: 14527595]
- Rudebeck PH, Walton ME, Smyth AN, Bannerman DM, Rushworth MF. Separate neural pathways process different decision costs. *Nat Neurosci*. 2006; 9:1161–1168. [PubMed: 16921368]
- Rushworth MF, Behrens TE, Rudebeck PH, Walton ME. Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. *Trends Cogn Sci*. 2007; 11:168–176. [PubMed: 17337237]
- Rushworth MF, Walton ME, Kennerley SW, Bannerman DM. Action sets and decisions in the medial frontal cortex. *Trends Cogn Sci*. 2004; 8:410–417. [PubMed: 15350242]
- Russell V, Allie S, Wiggins T. Increased noradrenergic activity in prefrontal cortex slices of an animal model for attention-deficit hyperactivity disorder – the spontaneously hypertensive rat. *Behav Brain Res*. 2000; 117:69–74. [PubMed: 11099759]
- Saunders B, Farag N, Vincent AS, Collins FL, Sorocco KH, Lovallo WR. Impulsive errors on a no-nogo reaction time task: disinhibitory traits in relation to a family history of alcoholism. *Alcohol Clin Exp Res*. 2008; 32:888–894. [PubMed: 18373725]
- Schachar R, Logan GD, Robaey P, Chen S, Ickowicz A, Barr C. Restraint and cancellation: multiple inhibition deficits in attention deficit hyperactivity disorder. *J Abnorm Child Psychol*. 2001; 35:229–238. [PubMed: 17351752]

- Schweighofer N, Tanaka S, Doya K. Serotonin and the evaluation of future rewards: theory, experiments, and possible neural mechanisms. *Ann N Y Acad Sci.* 2007; 1104:289–300. [PubMed: 17360806]
- Shaffer HJ, LaPlante DA, LaBrie RA, Kidman RC, Donato AN, Stanton MV. Toward a syndrome model of addiction: multiple expressions, common etiology. *Harv Rev Psychiatry.* 2004; 12:367–374. [PubMed: 15764471]
- Simon TR, Swann AC, Powell KE, Potter LB, Kresnow M, O'Carroll PW. Characteristics of impulsive suicide attempts and attempters. *Suicide Life Threat Behav.* 2001; 32(Suppl 1):49–59. [PubMed: 11924695]
- Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science.* 2004; 303:1157–1162. [PubMed: 14976305]
- Slutske WS, Caspi A, Moffitt TE, Poulton R. Personality and problem gambling: a prospective study of a birth cohort of young adults. *Arch Gen Psychiatry.* 2005; 62:769–775. [PubMed: 15997018]
- Slutske WS, Eisen S, True WR, Lyons MJ, Goldberg J, Tsuang M. Common genetic vulnerability for pathological gambling and alcohol dependence in men. *Arch Gen Psychiatry.* 2000; 57:666–673. [PubMed: 10891037]
- Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D. Impulsivity and prefrontal hypometabolism in borderline personality disorder. *Psychiatry Res.* 2003; 123:153–163. [PubMed: 12928103]
- Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH. Fifty years of the Barratt Impulsiveness Scale: an update and review. *Pers Individ Diff.* 2009; 47:385–395.
- Steel Z, Blaszczyński A. Impulsivity, personality disorders and pathological gambling severity. *Addiction.* 1998; 93:895–905. [PubMed: 9744125]
- Stout JC, Busemeyer JR, Lin A, Grant SJ, Bonson KR. Cognitive modeling analysis of decision-making processes in cocaine abusers. *Psychon Bull Rev.* 2004; 11:742–747. [PubMed: 15581127]
- Strakowski SM, Fleck DE, DelBello MP, Adler CM, Shear PK, McElroy SL, et al. Characterizing impulsivity in mania. *Bipolar Disord.* 2009; 11:41–51. [PubMed: 19133965]
- Swann AC, Anderson JC, Dougherty DM, Moeller FG. Measurement of inter-episode impulsivity in bipolar disorder. *Psych Res.* 2001; 101:195–197.
- Swann AC, Birnbaum D, Jagar AA, Dougherty DM, Moeller FG. Acute yohimbine increases laboratory-measured impulsivity in normal subjects. *Biol Psychiatry.* 2005a; 57:1209–1211. [PubMed: 15866563]
- Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. *Am J Psychiatry.* 2005b; 162:1680–1687. [PubMed: 16135628]
- Swann AC, Koslow SH, Katz MM, Maas JW, Javaid J, Secunda SK, et al. Lithium carbonate treatment of mania. Cerebrospinal fluid and urinary monoamine metabolites and treatment outcome. *Arch Gen Psych.* 1987; 44:345–354.
- Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG. Increased trait-like impulsivity and course of illness in bipolar disorder. *Bipolar Disord.* 2009a; 11:280–288. [PubMed: 19419385]
- Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG. Severity of bipolar disorder is associated with impairment of response inhibition. *J Affect Disord.* 2009b; 116:30–36. [PubMed: 19038460]
- Swann AC, Pazzaglia P, Nicholls A, Dougherty DM, Moeller FG. Impulsivity and phase of illness in bipolar disorder. *J Affect Disord.* 2003; 73:105–111. [PubMed: 12507743]
- Swann AC, Steinberg JL, Lijffijt M, Moeller FG. Impulsivity: differential relationship to depression and mania in bipolar disorder. *J Affect Disord.* 2008; 106:241–248. [PubMed: 17822778]
- Tataranni PA, Gautier JF, Chen K, Uecker A, Bandy D, Salbe AD, Pratley RE, Lawson M, Reiman EM, Ravussin E. Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc Natl Acad Sci USA.* 1999; 96:4569–4574. [PubMed: 10200303]

- Uslaner JM, Robinson TE. Subthalamic nucleus lesions increase impulsive action and decrease impulsive choice – mediation by enhanced incentive motivation? *Eur J Neurosci.* 2006; 24:2345–2354. [PubMed: 17074055]
- Verdejo-Garcia A, Bechara A, Recknor EC, Perez-Garcia M. Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. *J Int Neuropsychol Soc.* 2006; 12:405–415. [PubMed: 16903133]
- Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL, Bolla KI. The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug Alcohol Depend.* 2007; 90:2–11. [PubMed: 17367959]
- Verdejo-Garcia A, Lawrence AJ, Clark L. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neurosci Biobehav Rev.* 2008; 32:777–810. [PubMed: 18295884]
- Vitaro F, Arseneault L, Tremblay RE. Impulsivity predicts problem gambling in low SES adolescent males. *Addiction.* 1999; 94:565–575. [PubMed: 10605852]
- Volkow ND, Fowler JS, Wang GJ, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry.* 2004; 9:557–569. [PubMed: 15098002]
- Weijers HG, Wiesbeck GA, Boning J. Reflection-impulsivity, personality and performance: a psychometric and validity study of the Matching Familiar Figures Test in detoxified alcoholics. *Pers Individ Dif.* 2001; 31:731–754.
- Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G. Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. *Neuron.* 2003; 40:655–664. [PubMed: 14642287]
- Winstanley CA, Baunez C, Theobald DE, Robbins TW. Lesions to the subthalamic nucleus decrease impulsive choice but impair autoshaping in rats: the importance of the basal ganglia in Pavlovian conditioning and impulse control. *Eur J Neurosci.* 2005; 21:3107–3116. [PubMed: 15978020]
- Winstanley CA, Dalley JW, Theobald DE, Robbins TW. Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology.* 2003; 170:320–331. [PubMed: 12955303]
- Winstanley CA, Dalley JW, Theobald DE, Robbins TW. Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. *Neuropsychopharmacology.* 2004a; 29:1331–1343. [PubMed: 15054475]
- Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. *Clin Psychol Rev.* 2006a; 26:379–395. [PubMed: 16504359]
- Winstanley CA, Theobald DE, Cardinal RN, Robbins TW. Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *J Neurosci.* 2004b; 24:4718–4722. [PubMed: 15152031]
- Winstanley CA, Theobald DE, Dalley JW, Cardinal RN, Robbins TW. Double Dissociation between Serotonergic and Dopaminergic Modulation of Medial Prefrontal and Orbitofrontal Cortex during a Test of Impulsive Choice. *Cereb Cortex.* 2006b; 16:106–114. [PubMed: 15829733]
- Winstanley CA, Theobald DE, Dalley JW, Cardinal RN, Robbins TW. Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cereb Cortex.* 2006c; 16:106–114. [PubMed: 15829733]