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Striatal ups and downs: Their roles in vulnerability to addictions in humans

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Abstract

Susceptibility to addictive behaviors has been related to both increases and decreases in striatal function. Both profiles have been reported in humans as well as in animal models. Yet, the mechanisms underlying these opposing effects and the manner in which they relate to the behavioral development and expression of addiction remain unclear. In the present review of human studies, we describe a number of factors that could influence whether striatal hyper- or hypo-function is observed and propose a model that integrates the influence of these opposite responses on the expression of addiction related behaviors. Central to this model is the role played by the presence versus absence of addiction related cues and their ability to regulate responding to abused drugs and other rewards. Striatal function and incentive motivational states are increased in the presence of these cues and decreased in their absence. Alternations between these states might account for the progressive narrowing of interests as addictions develop and point to relevant processes to target in treatment.

Keywords

Basal ganglia; Conditioning; Dopamine; Drug addiction; Drug self-administration; Functional magnetic resonance imaging; Positron emission tomography; Sensitization; Striatum

1. Introduction

Two frequently contrasted theories propose that the development of addiction related behaviors reflects the hyper- versus hypo-activation of limbic reward systems. The debate is not new (e.g., Wikler, 1948, 1973; Vogel et al., 1948). Nor are the positions irreconcilable. Recent evidence raises the possibility that the expression of hyper- versus hypo-active incentive motivational states might reflect, in significant part, the presence versus absence of addiction related cues (Leyton and Vezina, 2012; see also Anagnostaras and Robinson, 1996; Anagnostaras et al., 2002; Stewart and Vezina, 1988, 1991; Vezina and Leyton, 2009). The present review focuses on the evidence for these alternating states in humans, the possibility that individuals may differ in their susceptibility to them, and the role that addiction related cues play in their expression. Although considered in the human clinical setting, many of the ideas discussed here have been tested over the last thirty years in some detail in preclinical drug sensitization experiments. The processes identified in these studies

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could have particular bearing for our understanding of the role played by addiction related cues in the generation of subjective and behavioral states in humans. We thus begin with a brief review of this literature before turning to a systematic treatment of the evidence in humans.

2. Preclinical studies in laboratory animals

Psychostimulant drugs like amphetamine, cocaine, and nicotine have long been known to produce their behavioral activating and motivating effects by stimulating the mesoaccumbens dopamine (DA) system. Many preclinical studies, mostly in rodents, have studied the effects of repeated exposure to these drugs on biochemistry and behavior. Of the different consequences of drug exposure assessed, two have emerged that have particular relevance for our understanding of excessive drug taking: the development of sensitization to the behavioral stimulant and incentive motivational effects of drugs and the formation of conditioned associations between these drug effects and various environmental stimuli. Although separate phenomena, these two consequences of drug exposure are known to interact as outlined below. It is the nature of this interaction that may be particularly informative for understanding how addiction related cues can influence the generation of subjective and behavioral states in humans.

An extensive preclinical literature now indicates that repeated intermittent exposure to psychostimulant drugs enhances not only the locomotor and brain DA activating effects they produce but more importantly the amount of work animals will emit to obtain and self-administer the drug (Mendrek et al., 1998; Vezina, 2004; Vezina et al., 2007). These effects are persistent (they are observed weeks to months after drug exposure in rodents; Hamamura et al., 1991; Paulson et al., 1991; Suto et al., 2004; Vezina et al., 2002), there is evidence that they increase in magnitude with the passage of time (Vanderschuren and Kalivas, 2000; Vezina, 2007), and they are observed following intermittent exposure (Robinson and Becker, 1986; Zimmer et al., 2012), a pattern often associated with initial exposure to the drug and initiation of drug use. Together, these findings support the proposal that sensitization of mesoaccumbens DA neuron reactivity may underlie the transition from sporadic experimentation to more frequent drug use and substance related problems (Robinson and Berridge, 1993, 2003).

An equally longstanding preclinical literature supports the importance of conditioned associations between stimulant drug effects and environmental contextual stimuli in drug seeking and self-administration (Stewart et al., 1984). The ability of drug paired stimuli to elicit conditioned locomotion (Stewart and Eikelboom, 1987) and forebrain DA release (Aragona et al., 2009; Di Ciano et al., 1998; Duvauchelle et al., 2000; Ito et al., 2000) is well established. Importantly, environmental stimuli previously paired with a psychostimulant drug slow extinction of responding for the drug (Tran-Nguyen et al., 1998) and reinstate drug seeking (de Wit and Stewart, 1981) in a manner that parallels their effects on DA transmission in the nucleus accumbens and amygdala (Weiss et al., 2000). The ability of these stimuli to reinstate drug seeking is long-lasting (Ciccocioppo et al., 2004) and becomes more intense with time (Grimm et al., 2001).

Because repeated systemic drug injections are administered in the presence of multiple environmental stimuli, the conditions are ripe for the simultaneous development of sensitization and conditioning of stimulant drug effects and for these two forms of plasticity to interact. While sensitization is known to develop non-associatively (Singer et al., 2009; Vezina and Stewart, 1990), there is evidence that its expression can come to be controlled by environmental stimuli previously paired or unpaired with the drug (Anagnostaras and Robinson, 1996; Anagnostaras et al., 2002; Stewart and Vezina, 1988, 1991; Vezina and

Leyton, 2009). Thus, rats previously exposed to the drug in one environment exhibit sensitized behavioral responses in this environment while rats previously exposed to the drug elsewhere do not. Indeed, rats that previously received the drug elsewhere show levels of responding on tests for sensitization that are comparable to those of rats administered the drug for the first time. This control over the expression of behavioral sensitization may be mediated, at least for contextual stimuli, by activity in a ventral hippocampus - nucleus accumbens – ventral pallidum – ventral tegmental area neuronal loop that regulates DA neuron firing in the latter site (Lodge and Grace, 2008).

Much of the evidence for the ability of environmental stimuli to control the expression of sensitization comes from experiments measuring locomotion (above references) although similar effects have been reported for drug-induced nucleus accumbens DA over-flow (Guillory et al., 2006; Reid et al., 1996). Importantly, such conditioned environmental stimuli have also been shown to control the expression of enhanced amphetamine self-administration and drug-induced reinstatement in rats previously exposed to nicotine (Cortright et al., 2012), again underscoring the critical role these stimuli play in the expression of enhanced drug self-administration and drug seeking.

The above preclinical findings notwithstanding, there has been some debate as to their generalizability to the human clinical arena. For example, no change or even reduced rather than augmented striatal responses to drugs have been reported in a number of influential studies of psychostimulant exposure conducted in drug self-administering non-human primates and addicted human subjects (e.g., Bradberry, 2007; Volkow et al., 1997). This has led to the proposal that increased DA reactivity associated with drug sensitization is of limited value to the human condition as a mechanism for drug abuse and other forms of pathology. We assess the merits of this argument below by reviewing the results of a large number of studies aimed at deciphering the effects of drugs and drug associated cues in humans. A number of factors emerge that may have potential importance for understanding how motivated behaviors are generated. Central among these is the presence versus absence of addiction related cues and their ability to regulate responding to abused drugs and other rewards. This factor in particular can facilitate the integration of a previously disparate group of findings in the animal and human literatures alike.

3. Studies in humans: subjective and behavioral states

3.1. Effects of cues

In substance abusers, exposure to stimulant drug associated cues elicits a wide range of subjective, behavioral and physiological responses (Carter and Tiffany, 1999; Childress et al., 1988; O'Brien et al., 1990). That these responses are drug-like is consistent with their ability to elicit incentive motivational states associated with the drug (Stewart et al., 1984; Robinson and Berridge, 2003)[1].

The elicited states include a narrowing of attentional focus toward the rewards and an increased propensity to pursue and approach them. The critical processes associated with activity in the striatum need not necessarily be conscious (Fischman, 1989; Tiffany, 1990; Lamb et al., 1991; Winkielman et al., 2005; Childress et al., 2008; Field et al., 2009; Perkins, 2009; Berridge, 2012; Waters et al., 2012); conscious craving may be more closely

[1]Stimuli associated with opiates and ethanol yield a more complex mix of drug-like and drug-opposite effects (Wikler, 1973; Eikelboom and Stewart, 1982; Stewart et al., 1984; O'Brien et al., 1998; Stewart, 2004). For discussions of how deficit states can augment incentive motivational states and the salience of appetitive cues, see Toates (1986), Hutcheson et al. (2001), and Berridge (2012). A role for dysphoric states in the maintenance of stimulant use has also been proposed in opponent process views of drug taking (Koob and Le Moal, 1997). These states are usually observed soon after prolonged and continuous exposure to drugs but their subsequent elicitation by conditioned cues has also been proposed to contribute to relapse (Siegel, 1979).

related to activity in cortical structures (Goldstein et al., 2009; de Lange et al., 2011). Nonetheless, self-reported craving is a commonly used proxy and ecological momentary assessments acquired with real-time electronic diaries confirm that exposure to drug cues, and their elicitation of craving states, commonly occur in the minutes and hours before new bouts of stimulant drug use (Epstein et al., 2009). Similarly, in laboratory studies, craving and reward-seeking behavior have been reported to increase following exposure to cues associated with amphetamine (Culbertson et al., 2010; Tolivar et al., 2010), cocaine (Childress et al., 1988, 1993), alcohol (George et al., 2001; Bragulat et al., 2008), cigarettes (Droungas et al., 1995; Carter and Tiffany, 2001; Wray et al., 2011), heroin (Fatseas et al., 2011; Zhao et al., 2012a), and natural rewards such as food (Jansen, 1998; Kelley and Berridge, 2002; Mahler and de Wit, 2010) and sex (Conaglen and Evans, 2006; Kim and Zauberman, in press).

Cues have more potent effects when subjects know that there will soon be an opportunity to use the drug (Carter and Tiffany, 2001; Dar et al., 2005; Juliano and Brandon, 1998). These, of course, are the usual circumstances under which the cues appear in the natural environment. A striking illustration of this phenomenon was recently reported in flight attendants. Smokers on either short (3–5.5 h) or long flights (8–13 h) developed cigarette cravings toward the end of the trip. Cravings at the end of the short flight were as strong as cravings at the end of the long flight and substantially higher than those seen at the shorter time-point during the long flight (Dar et al., 2010).

Drug related cues can also elicit behavioral effects. These include conditioned place preferences (Childs and de Wit, 2009, in press) and attentional biases (Cox et al., 2006; Hogarth et al., 2008; Field et al., 2009; Little et al., 2012), conditioned reinforcement (Foltin and Haney, 2000), accelerated initiation of drug use (Herman, 1974), as well as increased drug seeking (Panlilio et al., 2005; Hogarth et al., 2007) and self-administration (Herman, 1974; Droungas et al., 1995; Mucha et al., 1998; Hogarth et al., 2010).

3.2. Effects of drugs

As discussed above, a large animal literature indicates that the repeated administration of abused drugs can alter their effects. In humans, the best established change observed following repeated drug exposure has been transient tolerance to the subjective effects of stimulants (Brauer et al., 1996) and to the depressant effects of opiates and benzodiazepines (Hug, 1972)[2]. By comparison, the possibility that drug sensitization might occur in humans has been considered more controversial. Initial evidence came from observations made in the U.S. and Japan following the Second World War during episodes of heightened abuse of amphetamine-like drugs. Retrospective histories from this period suggested that repeated exposure to high doses of amphetamines (typically 100 mg or more) could lead to psychotic symptoms, including hallucinations and delusions (Connell, 1958; Ellinwood, 1967; Griffith et al., 1972; Sato, 1992; Sato et al., 1992). These effects could be reproduced in laboratory settings (Angrist & Gershon, 1970; Bell, 1973). The time course leading to the first psychotic episode was found to vary between individuals, an effect possibly related to dose, frequency of use, the co-abuse of other substances, and the presence of pre-existing vulnerability traits. Strikingly, periods of substance abuse were followed in some individuals by a long-lasting susceptibility to the re-emergence of psychotic symptoms after re-exposure to a much lower dose of the drug (Sato, 1992; Sato et al., 1992).

[2]Pharmacological tolerance refers to a decrease in a drug's potency or efficacy (i.e., maximal effect) with repeated exposure. Conversely, sensitization, also labeled reverse-tolerance, refers to an increase in drug potency or efficacy (sometimes indicated as a significant response to a previously ineffective dose). Both terms describe empirical observations; in and of themselves they do not connote mechanism.

Although intriguing, the above reports did not provide direct experimental evidence that repeated drug exposure could produce sensitization-like phenomena in humans. This evidence has been reported only more recently. In six of seven controlled laboratory studies in which participants received a minimum of 20 mg (p.o.) of *d*-amphetamine per session, sensitization of the drug's energizing effects was observed (Table 1). In the most recent study, evidence that this effect could come under environmental control was also seen. Subjects who received two doses of *d*-amphetamine in the same room reported a sensitized response to the second dose whereas those who received the second dose in a distinctively different room showed, if anything, evidence of tolerance (Childs and de Wit, in press).

It is noteworthy that the time courses for sensitization- and tolerance-like phenomena are different[3]. Whereas sensitization is a long-lasting, possibly even permanent phenomenon (Robinson and Becker, 1986; Boileau et al., 2006), tolerance is more transient (Vogel et al., 1948; Hug, 1972; Brauer et al., 1996). Indeed, a major precipitant of drug overdose and mortality stems from the ability of drug seeking states to be elicited long after tolerance has dissipated (Merrall et al., 2010).

3.3. Effects of cues and cues + drugs in different subject populations

In the sections below, we review the effects of drug cues and cues plus drugs. These effects are examined separately in healthy subjects without addictions, in subjects at risk for addictions, and in subjects with substance use disorders. Distinguishing between these populations is necessary as drugs and drug cues elicit different effects in different individuals. Since the effects of both acute and repeated drug exposure can interact with the particular characteristics an individual presents, they can provide insights into the factors that regulate the development and expression of motivated behaviors directed at obtaining and self-administering drugs of abuse. Indeed, as often noted, only some of the individuals who experiment with drugs develop a substance use disorder (Tsuang et al., 1998; Zinkernagel et al., 2001; Anthony, 2002; Agrawal et al., 2012; Kendler et al., 2012). Factors that have been identified to influence progression to addiction include personality traits (Ayduk et al., 2000; Conrod et al., 2000; Tarter et al., 2003), early life histories (Hyman et al., 2006; Enoch et al., 2010), ever-changing socio-cultural norms (Nutt, 2012), individual differences in drug specific metabolic enzymes (Ferguson and Tyndale, 2011), and additional heritable factors with unclear mechanisms. An implication of these observations for the study of addiction and addiction related processes is the need to identify and characterize effects that might occur preferentially within a subset of individuals (see also Saunders and Robinson, this issue).

4. Subjects without addictions: striatal activations

4.1. Effects of cues

Exposure to reward related events consistently activates the striatum in healthy humans (Knutson and Cooper, 2005). This has been studied in greatest detail in relation to monetary reward. In these studies, numerous types of stimuli are presented. These include (i) familiar cues that subjects already know are associated with the presence or absence of rewards, (ii) previously neutral cues that subjects learn about during the study, (iii) cues indicating that a reward will be presented either after passive waiting or after the emission of an operant response, and (iv) the reward itself. Each of these features can affect the magnitude of the striatal response and whether it is observed primarily within the ventral or dorsal striatum (O'Doherty et al., 2004; Knutson and Cooper, 2005). The focus of the present review is on

[3]Despite the different time courses for tolerance and sensitization, there can be temporal overlap since each of these adaptations can occur simultaneously in different systems, as in, for example, those regulating respiration versus those mediating incentive motivation.

how the magnitude of these striatal responses is influenced by individual and group differences.

In addition to monetary reward, healthy human subjects have been reported to show striatal activations following exposure to cues associated with food (Small et al., 2001; Beaver et al., 2006; Hommer et al., in press; Demos et al., 2012; Tang et al., 2012), sex (Hamann et al., 2004; Cloutier et al., 2008; Demos et al., 2012), and alcohol (Seo et al., 2011)[4]. There is evidence that these fMRI measured cerebral blood flow (CBF) responses may have been accompanied by an increase in DA release (Box 1). For example, striatal DA release measured in healthy subjects by positron emission tomography (PET) can correlate with fMRI measured activations (Schott et al., 2008). More importantly, evidence of DA release has been observed in healthy human subjects playing video games (Koepp et al., 1998) and following exposure to cues previously paired with monetary reward (Zald et al., 2004; Schott et al., 2008; Martin-Soelch et al., 2011; cf, Hakyemez et al., 2008), food (Volkow et al., 2002; Small et al., 2003), alcohol (Yoder et al., 2009) and amphetamine (Boileau et al., 2007).

The magnitude of the cue-induced DA response might vary with the expected certainty that a reward will be obtained. For example, in nonhuman primates, the largest increases in reward cue-induced DA cell firing are seen under conditions of maximal uncertainty (Fiorillo et al., 2003). Recent evidence raises the possibility that this effect of uncertainty can occur in humans as well: patients with Parkinson's disease exhibit a larger placebo-induced DA response if they are informed that the chance of receiving L-DOPA medication is 75% as compared to 100% (Lidstone et al., 2010)[5].

4.2. Effects of cues + drugs

As seen in laboratory animals, there is evidence for reciprocal interactions between drugs and reward related cues with each modulating the response to the other. In healthy human subjects, this has been observed most clearly in two studies where the dopaminergic effects of methylphenidate were augmented by the presence of salient appetitive cues (Volkow et al., 2002, 2004). In the first study, conducted in healthy food-deprived subjects (16–20 h abstinent), the combination of a low dose of methylphenidate (20 mg, p.o.) and food cues (visual, olfactory, taste) elicited greater striatal DA release and greater self-reported hunger than either alone (Volkow et al., 2002). Individual differences in DA release correlated with self-reported hunger and desire for food. In the second study, methylphenidate (20 mg, p.o.) elicited measureable striatal DA release only when it was paired with a salient mathematics task in which subjects could earn a monetary reward. The greater the DA release, the more interesting subjects reported the task to be (Volkow et al., 2004).

A third study provided the first explicit test of whether repeated drug administration could lead to DA sensitization in humans (Fig. 1). Healthy subjects were exposed to three doses of *d*-amphetamine (0.3 mg/kg, p.o.) on an every other day schedule. Following a two-week break, a fourth dose was given. The DA response to this fourth dose was significantly greater than that elicited by the first dose. A fifth dose, given a full year later, yielded an even larger effect (Boileau et al., 2006). Notably, all doses of *d*-amphetamine were

[4]Striatal activations can also occur following monetary losses (Kühn et al., 2011). In this study, participants were 154 14-year old video gamers. Frequent gamers (>9 h/week) exhibited a larger striatal response to monetary loss as measured by functional magnetic resonance imaging (fMRI) compared to less frequent gamers. Of note, stimuli indicative of loss are highly salient for gamers. Among professional gamers, greater striatal activation also predicts faster moves, an effect possibly reflecting an enhanced ability of cues to engage approach mechanisms (Wan et al., 2011).

[5]These conditions of uncertain reward delivery simulate a core aspect of gambling. Moreover, in rodents, uncertain reward delivery can increase a cue's motivational potency (Robinson and Berridge, 2012) and lead to behavioral sensitization to an amphetamine challenge (Singer et al., 2012).

administered in the same environment (the PET apparatus), rendering the results obtained consistent with environment-specific sensitization. While this study did not determine whether DA sensitization could also have been expressed if the amphetamine had been administered elsewhere, two recent studies conducted in non-dependent stimulant drug users are consistent with the proposal that the presence versus absence of drug associated stimuli can indeed influence the magnitude of drug-induced DA responses. In the first study, individual differences in cocaine-induced increases in extracellular DA were predicted by lifetime histories of stimulant drug use on the street: the greater the past drug use, the greater the DA response (Cox et al., 2009). In this study, participants prepared, manipulated, and self-administered the drug in their usual fashion. That is, cocaine associated cues were clearly present and engaged with. By comparison, in a second very similar study, healthy, non-dependent stimulant drug users were administered a disguised dose of *d*-amphetamine. In this case, individual differences in DA release were negatively correlated with drug use: the greater the past drug use, the smaller the DA response (Casey et al., 2012). Since similar effects have been well characterized in studies conducted in laboratory animals (Anagnostaras and Robinson, 1996; Anagnostaras et al., 2002; Stewart and Vezina, 1988, 1991; Vezina and Leyton, 2009), a tempting though speculative interpretation of these findings is that the presence versus absence of discrete and contextual drug associated cues modulated the response to the unconditioned drug stimulus. Thus, the presence of salient reward related cues might enable enhanced dopaminergic responding to a pharmacological challenge; the absence of such cues might prevent the expression of enhanced DA responses.

4.3. Age related differences: implications for development

An emerging literature is drawing attention to differences in striatal responding to reward related stimuli in adolescents (13–15 years of age) relative to young adults (early 20s). For example, adolescents have been reported to exhibit larger striatal activation than adults when presented with a stimulus that signals the opportunity to respond for money (Geier et al., 2010) and in response to receipt of the reward (Ernst et al., 2005; Galvan et al., 2006). Moreover, among the adolescents, the greater the striatal response to these cues, the higher their sensation seeking personality trait scores and self-reported excitement (Bjork et al., 2008a)[6]. These age-related responses have been proposed to account for developmental differences in risk-taking and reward-seeking behaviors (Spear, 2011; Ernst and Fudge, 2009; Somerville et al., 2010). Indeed, there is evidence that these striatal effects have predictive validity. For example, among healthy undergraduates ($n = 58$), the larger the nucleus accumbens response to food cues, the more weight subjects gained at follow-up six months later; the larger the response to sex cues, the greater the amount of sexual activity (Demos et al., 2012).

5. Subjects at risk for addictions: striatal activations

Groups of individuals can be categorized according to their risk for addiction. Among the best established predictors are (i) a dense family history of substance use problems (Dawson et al., 1992; Merikangas et al., 1998; Stoltenberg et al., 1998), (ii) externalizing behavioral characteristics and impulsive, sensation seeking personality traits (Krueger, 1999; Kendler et

[6]There are also conditions when lower striatal responses are observed, although the results reported thus far are complex and the relevant determining factors remain unclear. For example, lower striatal responses have been observed in adolescents versus adults evaluating a cue prior to being able to respond to it (Geier et al., 2010). Similarly, while adolescents show larger responses than adults to rewards (Ernst et al., 2005; Galvan et al., 2006), the gain in striatal response between large versus small rewards ($5 versus 20 cents) has been reported to be less (Bjork et al., 2004). One interpretation is that adolescents exhibit larger striatal responses to rewards and reward paired cues but smaller responses to more distal cues requiring more elaborate evaluative processes.

al., 1997, 2003, Tarter et al., 2003), and (iii) subjective and behavioral responses to a drug challenge (Schuckit, 1980; de Wit and Phillips, 2012).

5.1. Effects of cues

A small literature describes responses to rewards and reward related cues in subjects at risk for substance use disorders (see Tables 2 and 3). For example, compared to healthy low risk controls, larger striatal responses have been observed in subjects at familial risk for alcoholism when performing the Iowa Gambling Task (Acheson et al., 2009) and following exposure to alcohol odors (Kareken et al., 2004; Oberlin et al., 2012). In comparison, in studies where unfamiliar or otherwise neutral monetary reward cues were presented, high-risk populations exhibit smaller striatal responses than healthy controls (Andrews et al., 2011; Schneider et al., 2012; Yau et al., 2012).

5.2. Effects of cues + drugs

There is evidence that the effects of drugs and drug associated cues can interact in subjects at risk for addictions. In non-dependent heavy drinking cigarette chippers, for example, alcohol ingestion was found to increase the striatal response to cigarette cues (King et al., 2010). Conversely, there is evidence that cues can augment the effects of drugs. In subjects at elevated risk for addictions, striatal DA responses were augmented relative to low-risk subjects when the substance was ingested in the usual fashion (Setiawan et al., 2010) but diminished when the drug was administered in the absence of drug related cues (Casey et al., 2012). The blunted response reflected both a familial trait and an effect of past drug use: the greater the lifetime history of drug use, the smaller the DA response (Casey et al., 2012). The effects of familial trait and past drug use were independent. This was demonstrated in two ways. First, a control group was included consisting of stimulant drug using subjects matched on substance use to the high-risk subjects but lacking a family history of drug use problems. The high risk subjects with a family history of substance use disorders exhibited lower DA release than either this “low risk” drug using group or stimulant drug naïve subjects. Second, including drug use histories as a potential confounding variable in the statistical analyses did not diminish the contribution of family history. That is, both family and drug use histories produced the same effect but acted as independent contributors.

6. Subjects with substance use disorders: striatal activations

6.1. Effects of cues

Two recent meta-analyses independently concluded that the striatum is consistently activated by exposure to drug-related cues in subjects meeting diagnostic criteria for substance use disorders (Chase et al., 2011; Tang et al., 2012). These responses are stable (Schacht et al., 2011) and elevated, as compared to non-substance abusers. For example, compared to light social drinkers, dependent drinkers have been reported to exhibit greater alcohol cue-induced striatal activation (Vollstädt-Klein et al., 2010; Ihssen et al., 2011): the greater the striatal response, the greater the cue-induced attentional biases (Vollstädt-Klein et al., 2011) and the more severe the obsessive-compulsive drinking symptoms (Vollstädt-Klein et al., 2010). Similarly, in a large study of 326 heavy drinkers, the greater the alcohol cue-induced striatal activation, the greater the severity of alcohol use problems (Claus et al., 2011)[7].

[7]A recent case study illustrates how increases and decreases in striatal activity can co-vary with drug-seeking behavior and addiction. A severely alcoholic patient received sessions of transcranial magnetic stimulation (TMS) of the dorsal anterior cingulate cortex. Regional brain activity and self-reported craving were measured simultaneously. As expected, alcohol cue-induced craving was associated with increased activity in the nucleus accumbens. Strikingly, TMS decreased both the craving and the cue-induced activation of the nucleus accumbens, effects that were maintained for three months (De Ridder et al., 2011).

There is evidence that the above striatal activations may have been accompanied by an increase in DA release. Changes in PET tracer binding values indicative of striatal DA release have been observed following exposure to cues associated with cocaine (Volkow et al., 2006; Wong et al., 2006; Fotros et al., 2012) and heroin (Zijlstra et al., 2008). The greater the cue-induced DA release, the greater the craving (Volkow et al., 2006; Wong et al., 2006; Zijlstra et al., 2008; Fotros et al., 2012).

As seen in other populations, there is also evidence in those with substance use disorders that striatal activations are blunted rather than augmented when addiction related cues are absent. Compared to control subjects, blunted striatal activations occur in response to pictures of food in alcoholics (Ihssen et al., 2011) and to unfamiliar or otherwise neutral monetary reward cues in smokers (Peters et al., 2011) and detoxified alcoholics (Wrase et al., 2007; Beck et al., 2009; cf Bjork et al., 2008b).

6.2. Effects of cues + drugs

In subjects with substance use disorders, stimulant drug-induced striatal DA responses have been reported to be markedly reduced when compared to those observed in healthy controls (Volkow et al., 1997, 2007; Martinez et al., 2005, 2007, 2011, 2012; Wang et al., 2012; Thompson et al., in press; cf Urban et al., 2012; see Tables 2 and 3). These reductions may possibly aggravate the clinical picture. The lower the DA response, the greater the stimulant drug self-administration observed in separate sessions where the drug and its associated cues were made available (Martinez et al., 2007) and the worse the clinical outcome at follow-up (Martinez et al., 2011; Wang et al., 2012).

Notably, however, in all of the above studies, DA release was measured in the absence of drug cues. This raises the possibility that, even in late stage addiction, the reduced DA responses observed reflect, at least in part, either the absence of drug associated stimuli necessary to enable the expression of enhanced dopaminergic responding or the presence of drug unpaired stimuli capable of inhibiting this response (Vezina and Leyton, 2009). We are aware of only one study that has tested this hypothesis explicitly. In this study, cocaine dependent subjects were administered amphetamine on test sessions with or without drug cues present (videos of actors simulating drug use). Compared to the test session conducted without drug cues, the presence of drug cues actually diminished the DA response further (Volkow et al., 2008), an effect opposite in direction to what had been predicted by the authors. This observation nonetheless adds to the evidence that environmental cues can modulate the pharmacological effects of a stimulant drug challenge. Moreover, as the authors noted, since the cues did not genuinely predict that drug would become available, there may have been a reward prediction error associated with diminished DA release (Schultz et al., 1997; Yoder et al., 2009). This interpretation, though, remains speculative until more studies explicitly testing the proposition are reported. Other factors that might lead to decreased drug-evoked DA release in substance dependent populations include neurotoxic effects of extensive drug use (Little et al., 2003, 2009) and pre-existing risk traits (Casey et al., 2012). Methodological limitations may also be relevant. As noted by Narendran and Martinez (2008), reduced dopaminergic responding could also reflect decreases in D2 or D3 DA receptor affinity, decreases in the ratio of D3 to D2 DA receptors, or an increase in resting baseline DA levels. Preliminary attempts to address some of these possibilities, though, suggest that stimulant drug addicts, tested under the same conditions as in the above studies, have lower rather than higher resting levels of DA (Martinez et al., 2009) and higher rather than lower D3 DA receptor levels at least in D3 DA receptor rich brain regions such as the midbrain and globus pallidus (Boileau et al., 2012).

7. Subjects with non-substance addictions – gambling and binge eating disorders: striatal activations

Gambling (Frascella et al., 2010; Leeman and Potenza, 2012) and binge eating disorders[8] (Davis et al., 2011; Gearhardt et al., 2011) have been proposed to be forms of addiction. Both groups are at elevated risk for substance use disorders, yet some of the affected individuals do not use drugs or alcohol extensively. Studies in these populations with non-substance addictions thus have the potential to shed light on mechanisms relevant to perturbed reward seeking behaviors in isolation from the effects produced by drugs themselves.

In fMRI studies, increased striatal activations have been observed in problem gamblers, as compared to non-gamblers, following exposure to playing cards associated with monetary reward (van Holst et al., 2012). In contrast, either blunted (Balodis et al., 2012; Miedl et al., 2012; cf Reuter et al., 2005) or normal striatal responses (de Ruiter et al., 2009) have been reported following exposure to unfamiliar or otherwise neutral monetary reward cues (see Tables 2 and 3).

The results of PET [^{11}C]raclopride studies suggest that striatal DA responses follow the same pattern. For example, increased striatal DA responses have been observed to (i) a realistic gambling task in patients with severe pathological gambling (Joutsa et al., 2012), (ii) familiar gambling cues plus L-DOPA in patients with comorbid Parkinson's disease and pathological gambling (Steeves et al., 2009), (iii) food stimuli presented to binge eaters (Wang et al., 2011), (iv) L-DOPA medication given to Parkinson's patients exhibiting various impulse control problems (Evans et al., 2006; O'Sullivan et al., 2011), and (v) the undisguised administration of *d*-amphetamine pills to gamblers (Payer et al., 2012). By comparison, blunted striatal DA responses have been observed following stimulant drug challenges administered without drug cues in patients with bulimia nervosa (Broft et al., 2012). Of note, the augmented DA responses may aggravate the clinical picture. Pathological gamblers who show greater striatal DA release have higher clinical severity scores (Joutsa et al., 2012), greater difficulty restraining from gambling (Payer et al., 2012), and poorer performance scores on the Iowa Gambling Task (Linnet et al., 2010, 2011).

8. Conclusions: treating the striatum – boost or block?

Addictions are complex, multi-factorial, and heterogeneous in origin and expression. The factors discussed in the present review will not account for all facets of the disease. At the neurobiological level alone, addictions involve more brain regions than the striatum and more neurotransmitters than DA. Nonetheless, the current view describes processes that can account for much of the variability in the literature. It can also improve our understanding of the role of addiction related cues in disease etiology, course and outcome.

The studies reviewed above suggest that, in humans, repeated exposure to motivationally intense stimuli can lead to conditioned and sensitized behavioral and neurobiological responses. As exposure accrues, these cues can also come to modulate responses to the rewards themselves. Striatal hyperactivation can occur when rewards and reward related cues are present. Striatal hypoactivation can occur when reward-paired cues are absent. Exposure to rewards in the presence of reward associated cues can produce synergistic effects, a co-occurrence that to date has been more common on the street than in the

[8]Binge eating disorders share various common features with substance use disorders and pathological gambling. Dysregulated reward seeking, disturbed impulse-control, and various other addictions are commonly co-morbid. Obesity also has been proposed to be a form of behavioral addiction, although this idea is more controversial. For a discussion of these issues, see Ziauddeen et al. (2012).

laboratory. Finally, the results reviewed here suggest that these conditioned processes might exert their effects not only at early stages of substance use but continue to do so during later stages of addiction as well.

These cue modulated effects are of more than academic interest. First, the situation-dependent, conditioned control of incentive motivational systems may account in large part for increased drive to obtain some rewards and decreased drive to obtain others, features that are prominent as addictions develop. Second, if the proposed processes continue to have the same effects once addictions are established, then the model also has implications for treatment. For example, multiple attempts have been made to block a presumed hyperactive (sensitized) DA system. Although the strategy has not been exhausted, double-blind, placebo controlled clinical trials with chronic neuroleptic medications have not proven to be effective (Grabowski et al., 2000; Kampman et al., 2003; Smelson et al., 2004; Reid et al., 2005). Alternatively, sharply increasing DA transmission is most likely a relapse precipitant (de Wit, 1996; Barrett et al., 2006). Each of these strategies in isolation may lack clinical efficacy because patients with addictions experience alternating periods of increased and decreased striatal activation (Fig. 2). Promising strategies may be better afforded by approaches that selectively target enhanced responding to the drug and its control by drug associated stimuli (Kim et al., 2005; Barrett et al., 2008; Venugopalan et al., 2011; Loweth et al., 2013) or that retrain the patient to orient toward other cues and rewards, as is achieved in attentional bias training (Attwood et al., 2008; Fadardi and Cox, 2009; Schoenmakers et al., 2010; Zhao et al., 2012b) and contingent management therapies (Dutra et al., 2008; Volpp et al., 2009). Slow release DA indirect agonist preparations have shown modest, though inconsistent, efficacy in some populations (Castells et al., 2010; Mariani et al., 2012). Selective DA D3 receptor antagonists and DA modulators are in development, and might prove helpful (Mugnaini et al., 2012; cf, Dodds et al., 2012).

Finally, recent evidence has raised the possibility that individual differences in susceptibility to assign incentive value to reward related cues might be a general and heritable trait, influencing vulnerability to addictions or demarcating a distinct neurobiological risk pathway (Flagel et al., 2011; Fotros et al., 2012; Mahler and de Wit, 2010; Saunders and Robinson, this issue). In the latter case, DA targeted treatments might benefit the hypothesized DA reactive subgroup preferentially. Consistent with the notion that striatal reactivity reflects a pre-existing trait, individual differences in various reward seeking and impulsivity traits are predicted by the magnitude of striatal fMRI BOLD (Beaver et al., 2006; Bjork et al., 2008a) and DA responses (Leyton et al., 2002; Boileau et al., 2003, 2006; Buckholtz et al., 2010a,b; Treadway et al., 2012). The DA signals appear to have behavioral significance. Decreasing DA transmission diminishes cocaine cue-induced craving (Berger et al., 1996; Leyton et al., 2005), attentional biases toward drug cues (Franken et al., 2004; Munafó et al., 2007; Hitsman et al., 2008), the tendency of reward paired cues to elicit preferential responding (Leyton et al., 2007), and the willingness to work for drug (Barrett et al., 2008; Venugopalan et al., 2011) and monetary rewards (Cawley et al., 2010). These observations are consistent with the view that it is increased rather than decreased DA transmission that precipitates individual bouts of drug use, an observation recently seen across levels of substance use and addiction (Venugopalan et al., 2011). Thus, identifying ways to modulate these DA responses in a therapeutically significant way remains, we would suggest, an important clinical goal.

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Box 1

During the past few decades, two main tools have been developed to measure activity in living human brain. In functional magnetic resonance imaging (fMRI) studies, regional brain activity is assessed by measuring changes in cerebral blood flow (CBF). As with all living tissues, increased activity requires increased blood flow to supply needed oxygen. Magnetically captured fMRI signals respond to changes in blood flow by exploiting the paramagnetic and diamagnetic properties of deoxygenated and oxygenated hemoglobin, respectively. Temporal resolution ranges from 100 ms to 2 s depending on whether a single brain slice or the whole brain is sampled. Anatomical resolution ranges from <1 to 3 mm^3, depending on the magnet size (Hernandez et al., 2001). This method lacks neurochemical specificity.

Positron emission tomography (PET) can also be used to measure brain activity, but it is based on different principles. Subjects are administered a radioactively labeled substance that can cross the blood brain barrier. The decaying tracer emits positrons that typically travel 0.2–7 mm before colliding with an electron. The collision produces gamma rays that travel in diametrically opposite directions leading to their simultaneous activation of coincidence detectors positioned around the subject's head. The subsequently processed signals provide information about magnitude with temporal and spatial properties. Labeled water permits the measure of CBF. The use of labeled tracers such as [^{11}C]raclopride (a D2/3 DA receptor antagonist) permits estimation of the availability of D2/3 DA receptors. When extracellular DA levels are increased, the availability of DA receptors for [^{11}C]raclopride is reduced. Although temporal (20 to 30 min) and anatomical (cm^3 range) resolution are modest, the method is well validated (Laruelle, 2000; Doudet and Holden, 2003).

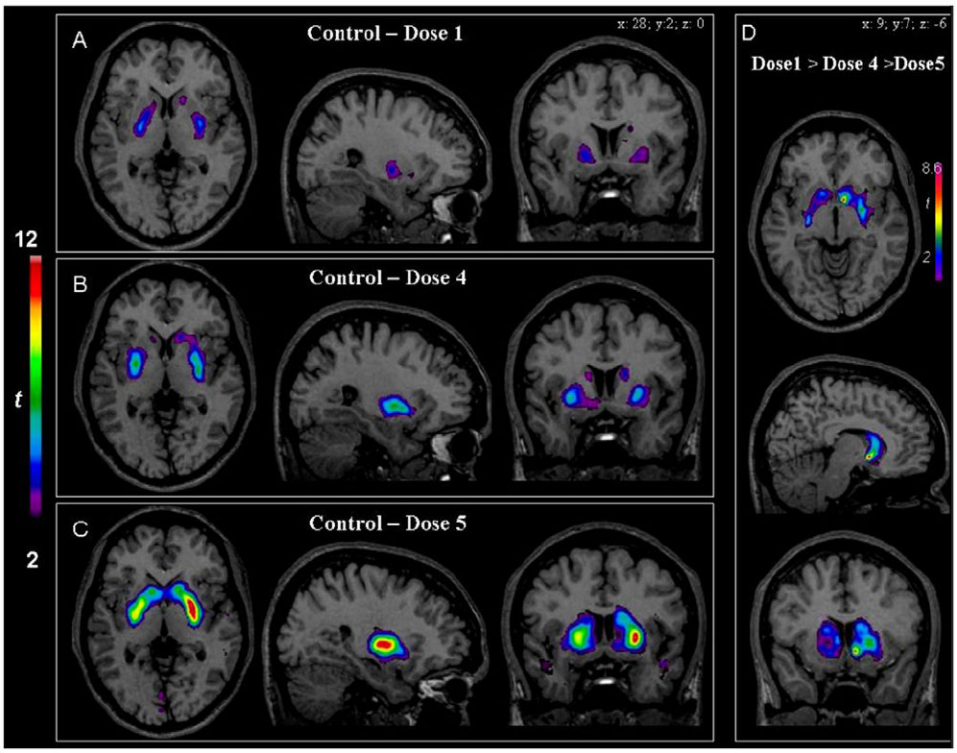

Fig. 1.

Amphetamine-induced DA sensitization in humans. Healthy male subjects received five doses of *d*-amphetamine (0.3 mg/kg, p.o.) while laying in a PET scanner. The first three doses were administered every second day. The fourth dose was given following a two-week abstinence period. The fifth dose was given one year later. The figure depicts the effects on striatal DA release, as indexed by changes in [^{11}C]raclopride binding, at dose 1 ((A) $n = 10$), dose 4 ((B) $n = 10$), and dose 5 ((C) $n = 7$). The higher the color coded t value, the greater the change in [^{11}C]raclopride binding. As illustrated in (D), linear regression analyses indicated that successive doses led to progressively larger responses. From Boileau et al. (2006).

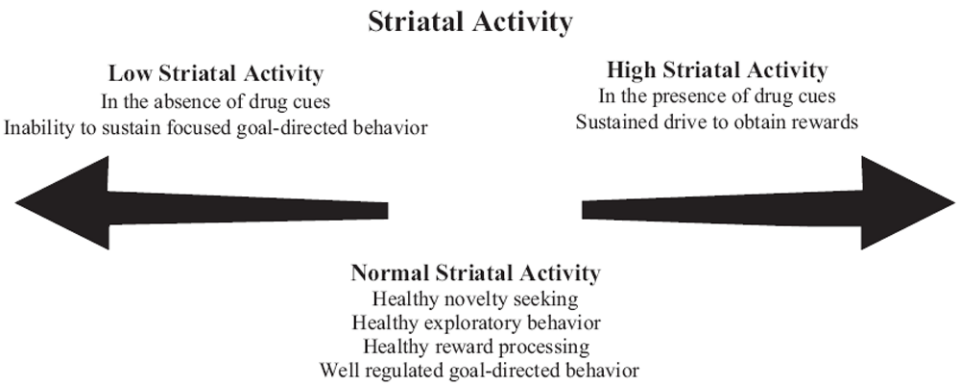

Fig. 2.

Model of striatal activation in addiction. Patients may experience periods of hyper- and hypo-activations of the striatum related to the presence versus absence of addiction related cues. In this model, chronic neuroleptic treatment would be predicted to decrease cue-induced activations of the striatum, a possibly helpful action, but also to aggravate the low striatal activity when addiction related cues are absent. Strategies that target the low or high striatal states without aggravating the other may be more effective.
Adapted from Leyton (2007).

Table 1

Dose-dependent development of sensitized responding to repeated *d*-amphetamine in healthy human subjects.

Amphetamine dose	No. of doses	Sensitization?	Reference
5.0 mg, p.o.	5 doses	No – mood, drug tablets chosen	Johanson and Uhlenhuth (1981)
10.0 mg, p.o.	6 doses	No – speech rate, smoking, stimulant effects, liking	Kelly et al. (1991)
20.0 mg, p.o.	2 doses	No – subjective and psychomotor effects	Wachtel and de Wit (1999)
~20 mg, p.o. (0.25 mg/kg)	2 doses	Yes – energy, eye-blink, mood, speech rate	Strakowski et al. (1996)
~20 mg, p.o. (0.25 mg/kg)	3 doses	Yes – energy, eye-blink	Strakowski and Sax (1998)
~20 mg, p.o. (0.25 mg/kg)	3 doses	Yes – energy, euphoria	Strakowski et al. (2001)
~20 mg, p.o. (0.30 mg/kg)	4 doses	Yes – energy, eye-blink	Boileau et al. (2006)
~20 mg, p.o. (0.30 mg/kg)	4 doses	Yes – energy, euphoria	O'Daly et al. (2011)
20.0 mg, p.o.	2 doses	Yes – stimulation, craving	Childs and de Wit (in press)

Table 2

fMRI BOLD striatal activations observed in human subjects in the presence and absence of reward associated cues. Subjects were individuals with susceptibilities to, or with current addiction disorders.

Subjects	Task/challenge	Results	Comment	Reference
Cues Present				
• 30 cocaine dependent patients in treatment • 36 healthy controls	Autobiographical scripts of drug use, stress and neutral experiences	Greater activation to drug scripts in male patients; greater activation to stress in female patients	Hospitalized patients receiving treatment for two weeks	Potenza et al. (2012)
• 24 heroin dependent patients in short-term abstinence (1 month) • 20 healthy controls	Images of heroin use or neutral stimuli	Greater activation in response to heroin images in patients	In these short-term abstinent patients, the longer the abstinence, the greater the activation	Li et al. (2012)
Heroin addicts • 17, short-term abstinence (1 month) • 17 long-term abstinence (1 year)	Images of heroin use or neutral stimuli	Heroin images activated striatum in short-term abstinent subjects and deactivated it in long-term abstinent subjects	Subjects able to sustain long-term abstinence might be able to inhibit responses to drug cues	Lou et al. (2012)
• 15 pathological gamblers • 16 healthy controls	Playing cards associated with monetary reward	Higher activation in gamblers		van Holst et al. (2012)
Heavy drinkers • with (n=17) and • without (n=13) family history of alcoholism	Alcohol odor	Higher activation in subjects with higher antisocial traits No effect of family history	Modest sample size; both groups consisted of heavy drinkers (18 drinks/week) with moderately high alcohol use problem scores	Oberlin et al. (2012)
• 20 cocaine dependent patients • 20 healthy controls	MID	Higher activation to reward notification in patients; higher response predicted worse treatment outcome	Treatment-seeking patients; the MID can be demanding, requiring sustained attention	Jia et al. (2011)
• 326 heavy drinkers	Alcohol taste cue	Positive correlation with alcohol use problems	No control group	Claus et al. (2011)
• 11 heavy drinkers • 12 light drinkers	Alcohol images	Higher activation in heavy drinkers	Small sample size	Ihssen et al. (2011)
Heavy drinkers • with (n=14) and • without (n=12) family history of alcoholism	Alcohol odors	No group differences	Small sample size; both groups consisted of heavy drinkers (17–18 drinks/week) with moderately high alcohol use problem scores	Kareken et al. (2010)
• 15 subjects with family history of alcoholism • 19 healthy controls	Iowa Gambling Task	Higher activation in family history positive group	Modest sample size	Acheson et al. (2009)
• 15 heroin dependent patients • 12 healthy controls	Heroin versus neutral videos	Higher activation in patients to heroin cues; lower responses to neutral cues	Modest sample size	Yang et al. (2009)

Subjects	Task/challenge	Results	Comment	Reference
• 12 opiate dependent patients • 17 healthy controls	Heroin versus pleasant versus neutral pictures	Only patients showed significant response to heroin cues; only controls showed significant response to pleasant non-drug cues	Modest sample size	Zijlstra et al. (2009)
• 23 alcohol dependent patients • 23 healthy controls	MID	Higher activation to reward notification in patients	Hospitalized patients receiving treatment	Bjork et al. (2008b)
• 37 heavy drinkers	Alcohol taste cue	Positive correlation with craving and alcohol use problems	No control group	Filbey et al. (2008)
• 16 detoxified alcohol dependent subjects • 16 healthy controls	Alcohol images + MID	Alcoholics showed greater activation to anticipation of alcohol cues and lower activation to non-alcoholic cues	Modest sample size	Wrase et al. (2007)
• 6 detoxified alcohol dependent patients • 6 healthy controls	Alcohol images	No effect in striatum	Small sample size; hospitalized patients receiving treatment	Lingford-Hughes et al. (2006)
• 12 pathological gamblers • 12 healthy controls	Card guessing game with electronic cards	Lower activation in gamblers	Small sample size; cues possibly not evocative of real cards	Reuter et al. (2005)
• 10 alcohol dependent subjects • 10 healthy controls	Alcohol sip + images	Activation in alcoholics, not controls; positive correlation between cue-induced craving and accumbens activation in alcoholics only	Small sample size	Myrick et al. (2004)
• 10 abstinent alcohol dependent subjects • 10 healthy controls	Alcohol images	Greater activation in alcoholics; strong activations predicted relapse	Small sample size	Grüsser et al. (2004)
• 4 alcohol dependent subjects • 4 healthy controls	Alcohol images	Higher activation in alcoholics; strong activations predicted rapid relapse	Small sample size	Braus et al. (2001)
• 17 cocaine abusers • 14 healthy controls	4-min videos of cocaine use, sex; neutral activity	Higher activity in cocaine abusers	Lower activity than controls in response to sex video	Garavan et al. (2000)
Cues Absent				
• 30 cocaine addicted subjects • 28 former cocaine addicted subjects • 31 healthy controls	Unfamiliar Domino game in which subjects gain or lose chips	Lower activation to gains in former cocaine addicted versus healthy and current addicted subjects; no difference between control and current addicted subjects		Hyatt et al. (2012)
• 14 pathological gamblers • 14 healthy controls	MID	Lower activation in gamblers during prospect and anticipation	Modest sample size	Balodis et al. (2012)
• 31 adolescents with problem substance use	MID	Lower activation in substance abusers during anticipation phase		Schneider et al. (2012)

Subjects	Task/challenge	Results	Comment	Reference
• 266 healthy controls				
• 20 children of alcoholics • 20 healthy controls	MID	Lower activation in children of alcoholics during anticipation phase	Only seen in subgroup that had not yet developed problem drinking	Yau et al. (2012)
• 16 pathological gamblers • 16 healthy controls	Delay discounting task	Negative correlation with gambling severity	Between group effects not reported	Miedl et al. (2012)
• 43 adolescent smokers • 43 healthy controls	MID	Lower activation in smokers during anticipation phase	Same response seen in subjects who smoked ≤ 10 cigarettes; thus, blunted response may be vulnerability trait	Peters et al. (2011)
• 30 subjects with family history of alcoholism • 19 healthy controls	MID	Lower activation in family history positive subjects during anticipation phase; higher activation during the prospect phase		Andrews et al. (2011)
• 14 heavy drinkers • 14 light drinkers	Intravenous ethanol (BAC=0.08)	Lower activation in heavy drinkers	Modest sample size	Gilman et al. (2012)
Parkinson's disease patients • with (n=9) • without (n=9) impulse-control disorders	Balloon Analog Risk Task	Lower activation in patients with impulse-control problems	Modest sample size	Rao et al. (2010)
• 19 problem gamblers • 19 smokers • 19 healthy controls	Monetary gain following exposure to previously neutral cues	No group differences		de Ruiter et al. (2009)
• 19 detoxed alcoholics • 19 healthy controls	MID	Lower activation in alcoholics during anticipation phase	In alcoholics, low striatal activation predicted high impulsivity scores	Beck et al. (2009)
• 13 children of alcoholics with high sensation seeking scores • 13 healthy adolescents	MID	Greater activation in high sensation seekers during anticipation phase	Modest sample size	Bjork et al. (2008a)
• 16 detoxified alcohol dependent subjects • 16 healthy controls	Alcohol images + MID	Alcoholics showed lower activations to MID monetary anticipation	High striatal responses also seen in response to alcohol cues	Wrase et al. (2007)
• 17 cocaine abusers • 14 healthy controls	4-min videos of cocaine use, sex; neutral activity	Lower activity than controls in response to sex video	Higher activity than controls in response to cocaine video	Garavan et al. (2000)

BAC: blood alcohol concentration. MID: monetary incentive delay task.

Table 3

PET [^{11}C]raclopride striatal responses observed in human subjects in the presence and absence of reward associated cues. Subjects were individuals with susceptibilities to, or with current addiction disorders.

Subjects	Task/challenge	Results	Comment	Reference
Cues Present				
• 12 pathological gamblers • 12 healthy controls	Slot machine gambling task	Higher DA response in severe gamblers	High DA response predicted greater gambling problem severity	Joutsa et al. (2012)
• 13 pathological gamblers • 12 healthy controls	Undisguised amphetamine pills	Higher DA release in gamblers	High DA response predicted more desire to gamble and greater difficulty restraining from gambling	Payer et al. (2012)
Obese subjects • with (n=10) or • without (n=8) binge eating disorder	Food smell and taste	Higher DA release in binge eaters	Modest sample size; DA release correlated with binge eating problems	Wang et al. (2011)
Parkinson's disease patients • with (n=11) or • without (n=7) impulse-control problems	Various reward related cues (images of appetizing food, sex, gambling, drugs etc.)	Higher DA release in impulsive patients	Modest sample size	O'Sullivan et al. (2011)
• 18 pathological gamblers • 16 healthy controls	Iowa Gambling Task	High DA release predicted greater excitement	No significant effect of group	Linnet et al. (2011)
• 16 pathological gamblers • 15 healthy controls	Iowa Gambling Task	High DA release predicted poorer performance	No significant effect of group	Linnet et al. (2010)
Heavy drinkers at • high (n=13) or • low-risk (n=13) for alcoholism	Alcohol ingestion	Higher DA response in subjects at high risk	Risk defined by (i) SHAS scores and (ii) reward-seeking personality traits	Setiawan et al. (2010)
Parkinson's disease patients • with (n=7) or • without (n=7) pathological gambling	L-DOPA + gambling task with cards	Higher DA release in gamblers	Small sample size	Steeves et al. (2009)
• 20 cocaine dependent patients	Methylphenidate (0, 20 mg, p.o.) with or without cocaine videos	Lower DA response with drug videos	Cues did not predict receipt of reward; possible reward prediction error; no comparison group	Volkow et al. (2008)
Parkinson's disease patients • with (n=8) or	L-DOPA medication	Higher DA release in substance dependent patients	Small sample size	Evans et al. (2006)

Subjects	Task/challenge	Results	Comment	Reference
• without (n=8) substance dependence				
	Cues Absent			
• 11 patients with schizophrenia and a substance use disorder • 15 healthy controls	Amphetamine (0, 0.3 mg/kg, iv)	Lower DA release in patients		Thompson et al. (in press)
• 16 cannabis dependent patients • 16 healthy controls	Amphetamine 0, 0.3 mg/kg, iv)	No group differences	Earlier age of onset of cannabis use predicted lower DA response	Urban et al. (2012)
• 15 patients with bulimia nervosa • 14 healthy controls	Methylphenidate (0, 60 mg, po)	Lower DA release in patients	Low DA release predicted more frequent binge eating	Broft et al. (2012)
• 16 heroin dependent patients • 16 healthy controls	Methylphenidate (0, 60 mg, po)	Lower DA release in patients		Martinez et al. (2012)
• 24 cocaine dependent patients • 24 healthy controls	Methylphenidate (0, 60 mg, po)	Lower DA release in patients	Low DA release predicted poor treatment outcome	Martinez et al. (2011)
• 16 subjects at high familial risk for addictions • 15 subjects at low familial risk matched on drug use • 17 healthy subjects,	*d*-amphetamine (0, 0.3 mg/kg, po)	Lower DA release in high-risk subjects	Low DA release predicted by lifetime history of drug use	Casey et al. (2012)
• 24 cocaine dependent patients • 24 healthy controls	Methylphenidate (0, 60 mg, po)	Lower DA release in patients	Low DA release predicted choice of lab cocaine over money	Martinez et al. (2007)
• 20 alcohol dependent patients • 20 healthy controls	Methylphenidate (0, 0.5 mg/kg, iv)	Lower DA release in patients		Volkow et al. (2007)
• 15 alcoholic dependent patients • 15 healthy controls	Amphetamine (0, 0.3 mg/kg, iv)	Lower DA release in patients		Martinez et al. (2005)
• 20 cocaine dependent patients • 23 healthy controls	Methylphenidate (0, 0.5 mg/kg, iv)	Lower DA release in patients		Volkow et al. (1997)

DA: dopamine. SHAS: Subjective High Assessment Scale.