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# Reward, Interrupted: Inhibitory Control and Its Relevance to Addictions

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## Abstract

There are broad individual differences in the ability to voluntarily and effortfully suppress motivated, reward-seeking behaviors, and this review presents the hypothesis that these individual differences are relevant to addictive disorders. On one hand, cumulative experience with drug abuse appears to alter the molecular, cellular and circuit mechanisms that mediate inhibitory abilities, leading to increasingly uncontrolled patterns of drug-seeking and –taking. On the other, native inter-individual differences in inhibitory control are apparently a risk factor for aspects of drug-reinforced responding and substance use disorders. In both cases, the behavioral manifestation of poor inhibitory abilities is linked to relatively low striatal dopamine D2-like receptor availability, and evidence is accumulating for a more direct contribution of striatopallidal neurons to cognitive control processes. Mechanistic research is now identifying genes upstream of dopamine transmission that mediate these relationships, as well as the involvement of other neurotransmitter systems, acting alone and in concert with dopamine. The reviewed research stands poised to identify new mechanisms that can be targeted by pharmacotherapies and/or by behavioral interventions that are designed to prevent or treat addictive behaviors and associated behavioral pathology.

### Keywords

impulsivity; compulsivity; motivation; cognition; dopamine; executive function

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## 1. Motivated Actions and Inhibition

Like food/nutrients, water and sexual stimuli, drugs of abuse act as behavioral reinforcers, and humans and non-human animals are motivated to obtain them (Brady, 1991; Johanson, 1978; Spealman and Goldberg, 1978; Weeks, 1962). Since the work of Olds and Milner in the 1950s (Olds and Milner, 1954), an immense amount has been learned about the neural pathways that mediate reinforcement and reward and that allow drugs of abuse to support seeking and taking behaviors (Gardner, 2011; Haber and Knutson, 2010; Kalivas and Volkow, 2005; Kelley et al., 2002; Robbins et al., 1989; Sesack and Grace, 2010; Wise, 2002). Additionally, a recent major advance in the study of drug-reinforced behaviors has been the identification of both goal-directed (“impulsive”) and habitual (“compulsive”) aspects of drug-seeking and –taking and the characterization of the differential neural mechanisms that mediate each (Belin-Rauscent et al., 2012; Everitt et al., 2001).

While the motivation to obtain drugs or to engage in drug-directed responding has received intense study, the phenomenon of inhibitory control – or motivated interruption of reinforced responding – has received much less attention. Human beings are often motivated to completely abstain from taking drugs or to reduce their drug use because of the accumulated aversive consequences of drug consumption, because of the fear of social stigma or because of their own desire to achieve a healthier lifestyle. These attempts to avoid, cut down or terminate drug seeking and consumption depend upon effortful, voluntary inhibition of the conditioned affective and behavioral reactions to drug-related cues and drugs themselves. The engagement in drug-seeking and –taking therefore depends upon the relative strength of both the motivation to use the drug and the motivation (and capacity) to resist it. Thus, while models that propose heightened (“sensitized”) motivation to obtain drugs as a function of drug experience are relevant to addiction (Robinson and Berridge, 1993, 2008), so are models that highlight addiction-related problems with the capacity for inhibitory control (Bechara and Martin, 2004; Garavan and Hester, 2007; Goldstein and Volkow, 2002; Izquierdo and Jentsch, 2012; Jentsch and Taylor, 1999a; Robinson and Berridge, 2003; Volkow et al., 2004). This review aims to discuss literature supporting the hypothesis that inter-individual differences in striatonigral, D2-like receptor expressing neurons – whether genetically or environmentally influenced – predispose individuals to the development of addiction by influencing inhibitory control abilities. Further, in addition to earlier work that predominantly highlighted a role of the prefrontal cortex in executive control processes, we discuss evidence suggesting a direct role of striatal neurons in regulating these processes.

## 2. Inhibitory Control Deficits in Addiction

It is well-established that addictions are associated with reduced inhibitory control (Ersche et al., 2011; Ersche et al., 2008; Ersche et al., 2012; Fillmore and Rush, 2002, 2006; Lee et al., 2009; Monterosso et al., 2005). These investigations involved the use of a variety of laboratory measures conventionally thought to measure inhibitory control over pre-potent or impulsive responses, including self-report measures of impulsivity (Patton et al., 1995), the stop signal reaction time task, multiple choice serial reaction time tasks and reversal learning procedures (Table 1). While these measures and tasks are conceptually and procedurally

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distinct, they appear to uncover similar neural and molecular mechanisms and have similar informative value in some cases (discussed below) and are therefore referenced collectively here.

Of importance, however, the extent to which these deficits predate drug use (representing a biobehavioral marker of susceptibility), and/or consequences of experience with the pharmacological effects of the drug, is less clear. Another model, yet to be tested, is that some people are at genetic risk for drug-induced deficits in inhibitory control; a gene by environment (drug) interaction of this sort may reveal itself through escalating neuroadaptations in inhibitory control circuitry with prolonged exposure to the pharmacodynamic effects of drugs of abuse.

## 2.1 Inhibitory Deficits Result from Drug Use

It is quite clear that long-term exposure to drugs of abuse in animals is sufficient to produce inhibitory control deficits (Calu et al., 2007; Jentsch et al., 2002; Jentsch et al., 1997a; Jentsch et al., 2000; Jentsch et al., 1997b; Krueger et al., 2009; Parsegian et al., 2011; Schoenbaum et al., 2004). Nonetheless, much remains unknown about the details of this phenomenon. For example, do individual drugs of abuse (stimulants vs. alcohol vs. tobacco vs. opiates) vary in their propensity to produce inhibitory control deficits (Ersche et al., 2008)? Are particular patterns of drug intake associated with greater impairment? Do various forms of inhibitory control (suppression of behavior vs. emotions vs. intrusive thoughts) show greater sensitivity to drug-induced deficits (Calu et al., 2007; Parsegian et al., 2011; Schoenbaum et al., 2004)? Though the general idea that chronic drug experience causes these behavioral abnormalities is now unambiguous, a large set of questions must still be answered.

Evidence is mounting that drug-induced deficits in inhibitory control are linked with neuroadaptations in dopamine D2-like receptor signaling (Lee et al., 2009; Volkow et al., 2001; Volkow et al., 1993; Volkow et al., 1996; Wang et al., 1997). D2-like receptor availability was first shown to be decreased within the striatum of cocaine abusers twenty years ago (Volkow et al., 1993). Since then, these findings have been recapitulated in a number of affected populations, including alcohol (Volkow et al., 1996), nicotine (Fehr et al., 2008), methamphetamine (Lee et al., 2009; Volkow et al., 2001), and opiate abusers (Wang et al., 1997), suggesting that these alterations are a common substrate underlying addiction. In support of the notion that these differences represent neuroadaptations produced by drugs of abuse, it has been demonstrated using non-human primates that both the chronic self-administration of cocaine (Moore et al., 1998; Nader et al., 2006) and chronic experimenter administered methamphetamine (Groman et al., 2012) are sufficient to produce long-lasting decreases in striatal D2-like receptor availability.

Pharmacological studies have provided a causal link between striatal D2-like receptors and inhibitory control and suggest that decreased receptor density may directly influence the inhibitory control deficits seen in addiction. The dopamine D2/D3 receptor antagonist raclopride has been found to impair reversal learning performance in monkeys (Lee et al., 2007). Conversely, the performance of cocaine addicts on the reversal learning task was improved by administration of the D2/D3 receptor agonist, pramipexole, and this change

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was correlated with task-related changes in striatal activity (Ersche et al., 2011). In addition, the systemic injection of the D2-like receptor agonist, quinpirole, has been shown to decrease the number of premature responses that rats make in the 5-chioce serial reaction time task (5-CSRT), possibly reflecting a greater ability to refrain from impulsive actions (Fernando et al., 2012). Lastly, direct manipulations of striatal D2-like receptors alter both 5-CSRT and reversal learning performance (Besson et al., 2010; Haluk and Floresco, 2009).

In summary, the chronic administration of drugs of abuse appears sufficient to produce reductions in both striatal D2-like receptors and inhibitory control processes, and reductions in D2-like receptors may contribute causally to the latter behavioral difference.

### 2. 2. Inhibitory Control Deficits Index Susceptibility for Addictions

Despite strong evidence that deficits in inhibitory control may result from drug use, longitudinal and family studies have made it increasingly apparent that reduced inhibitory control might also serve as a genetically determined risk factor for addiction. Children less capable of regulating their own behavior appear to be at a heightened risk for developing a substance use disorder later in life. For instance, male three year olds designated as undercontrolled, irritable, and impulsive were more likely to be diagnosed with alcohol dependence at age 21 than well-adjusted children (Caspi et al., 1996), and disinhibition at ages 10–12 has been shown to predict substance use disorders at age 19 in males (Tarter et al., 2003). Additionally, the Eysenck and Cloninger personality traits of psychoticism and novelty seeking – which both comprise impulsive and disinhibited tendencies – were shown to prospectively predict substance use disorders in college students (Sher et al., 2000). Lastly, attention deficit hyperactivity disorder, which is in essence a disorder of self-control, has been associated with the development of substance abuse disorders (Groman et al., 2009; Mannuzza et al., 1993, 1998; Wilens et al., 2011).

The idea that reduced inhibitory control is a genetic or familial risk factor for addiction would be quantified by an increased incidence of this trait as a function of genetic proximity to a substance use disorder. A number of studies have now found that measures related to behavioral control are affected in the family members of affected probands (Acheson et al., 2011a; Acheson et al., 2011b; Dawes et al., 1997; Ersche et al., 2012; Nigg et al., 2004). These studies show that both the children of addicts – who are themselves at high risk for developing the disorder – as well as their unaffected siblings, display lower levels of inhibitory control than those that are not in close relation to the disorder.

Data from preclinical research further suggest that measures of inhibitory control predict patterns of drug use and that these differences are genetically determined. Rats with a propensity to engage in high levels of premature responding in a choice reaction time task self-administer greater amounts of cocaine and transition to compulsive patterns of drug intake more readily (Belin et al., 2008; Dalley et al., 2007). Additionally, recent work in our laboratory using inbred mice has shown that performance on the reversal learning task is moderately heritable (Laughlin et al., 2011). Furthermore, inbred mouse strains with poor inhibitory control performance also self-administer greater amounts of cocaine and are more sensitive to cocaine's locomotor-activating properties, suggesting a genetic link between inhibitory control and substance use (Cervantes et al., 2013).

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Hypothetically, these relationships may depend upon the fact that the neural circuits mediating inhibitory control and drug reinforcement are both - perhaps independently - controlled by dopamine D2-like receptors. Recently, it has become clear that individual differences in dopamine D2-like receptor availability, as assessed via PET imaging, predict trait-like differences in inhibitory control in multiple species, and across multiple behavioral tasks. In both rats and mice, a poor inhibitory control phenotype is linked to low dopamine D2-like receptor availability and/or function (Dalley et al., 2007; Laughlin et al., 2011). In non-human primates, reversal learning competency also was positively associated with D2-like receptor availability (Groman et al., 2011). Importantly, unlike the previous rodent studies in which receptor differences were only noted between groups, likely owing to limited genetic variability in rodent lines, this work showed a continuous relationship between the two traits. Lastly, studies on humans have since found that greater D2-like receptor availability predicts greater inhibitory control capabilities using both the stop signal reaction time task and the Barratt Impulsiveness Scale (Ghahremani et al., 2012; Lee et al., 2009; Reeves et al., 2012). Taken as a whole, these studies provide exceedingly consistent evidence that decreased D2-like receptor availability predicts a diminished capacity for control over behavior, and further suggest that these differences contribute to the development of substance dependence.

## 3. The Neural Circuitry of Inhibitory Control

Earlier models linking inhibitory control deficits to addiction proposed a central role for catecholamine transmitters in regulating frontostriatal circuits (Jentsch and Taylor, 1999b). This hypothesis was supported by findings that substance dependent individuals displayed reduced prefrontal glucose utilization (Volkow et al., 1993; Volkow et al., 1991; Volkow et al., 1992), that damage to prefrontal regions in humans and animals resulted in disinhibited and perseverative behaviors (Butter, 1969; Dias et al., 1996, 1997; Iversen and Mishkin, 1970; Milner, 1963; Robbins, 1996), and that pharmacological manipulations that alter catelcholamines in the prefrontal cortex alter indices of executive control (Charrier and Thiébot, 1996; Ridley et al., 1981a; Ridley et al., 1981b; Roberts et al., 1994; Sokolowski and Salamone, 1994; Taylor et al., 1990). Over the course of past decade support for this hypothesis has grown, with an increasingly large number of human imaging studies showing structural abnormalities in the prefrontal cortex of substance dependent individuals (Brody et al., 2004; Franklin et al., 2002; Liu et al., 1998; Matochik et al., 2003; Tanabe et al., 2009; Thompson et al., 2004), in addition to altered recruitment of prefrontal brain regions in tasks measuring response inhibition (Bolla et al., 2003; Courtney et al., 2012; Ersche et al., 2011; Li et al., 2009; Nestor et al., 2011).

Because the striatum remains an important efferent target of prefrontal cortical neurons, and because striatal neurons are themselves regulated by catecholamine transmitters, it remains possible that dysregulation within the prefrontal cortex and/or striatum combine to produce the patterns of inhibitory control problems found in addictions.

Earlier theories of frontostriatal dysfunction in addiction hypothesized that alterations in the striatum were more likely to be involved in motivational components of addiction, whereas those in the prefrontal cortex subserved executive functions (Bolla et al., 1998; Jentsch and

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Taylor, 1999b). Such ideas are consistent with a rich literature on mesolimbic dopamine systems supporting drug reinforcement and motivational output (Koob and Swerdlow, 1988; Robbins et al., 1989; Roberts et al., 1980; Robinson and Berridge, 1993; Salamone, 1992; Salamone and Correa, 2012), and in the role of the striatum in acquiring and executing skilled motor patterns (Graybiel, 1998; Hikosaka, 1991; Lacourse et al., 2005; Lovinger, 2010; Salamone, 1992; Yin et al., 2009). These sentiments have been expanded into popular Thorndikian learning models wherein the striatum serves to establish behaviors as habitual and compulsive, becoming independent of voluntary initiation (Everitt and Robbins, 2005; Hogarth et al., 2012; Shiflett and Balleine, 2011; Yin and Knowlton, 2006).

While there is a great deal of evidence to support such theories, there is a growing body of evidence that suggests that striatal neurons cooperate with frontal cortical systems in inhibitory control. A number of studies using both non-human primates and rodents have now shown that both the ablation and inactivation of medial portions of the striatum selectively impair inhibitory control in reversal learning tasks (Castañé et al., 2010; Clarke et al., 2008; Ragozzino et al., 2002). Additionally, 6-hydroxydopamine lesions of this same region have been shown to impair reversal learning performance, pointing to the importance of dopaminergic innervation of this region (Clarke et al., 2011; O’Neill and Brown, 2007b). Lastly, a recent study utilizing optogenetic stimulation to elucidate the role of striatal neurons at distinct choice points in a two-choice reversal task showed that activation of dorsomedial striatal neurons is capable of biasing choice behavior, but that this bias is greatest under conditions of uncertainty, immediately following a switch in reward contingencies (Tai et al., 2012). Collectively, these studies highlight a role for the striatum in the ability to suppress prepotent actions and adaptively shift behavior in the face of changing environmental contingencies.

Striatal neurons play a long recognized role in reward, reinforcement and motivational processes (Balleine and O’Doherty, 2010; Everitt and Robbins, 2013; Kelley, 2004; Pennartz et al., 2009; Richard et al., 2012; Salamone and Correa, 2002). A logical question that arises, therefore, is whether striatal function affects inhibitory control abilities through a primary modulation of motivational state or by being the site of action of top-down cortical control over behavior in a manner that is relatively independent of incentive or hedonic processing? Some data supports the notion that dopamine-modulated striatal systems contribute directly to both processes; dopaminergic manipulations of the ventral striatum have been shown to alter both inhibitory control and motivation (Besson et al., 2010; Cousins et al., 1993; Haluk and Floresco, 2009). On the other hand, dissociable control of these two processes has also been revealed. While dopamine depletions of the rodent ventral striatum have been shown to produce robust motivational deficits, depleting dopamine in the medial striatum has been shown to leave motivation to work for a preferred food reward intact (Cousins et al., 1993). Moreover, dopamine depletions of the rodent dorsomedial striatum and homologous primate caudate nucleus impair reversal learning performance but do not concurrently alter response latencies, another way to index motivation during the reversal learning task (Clarke et al., 2011; Eagle et al., 2011; O’Neill and Brown, 2007a). The same has been found following excitotoxic lesions of this brain region (Clarke et al., 2008). These data could be construed as evidence that dopaminergic function in the striatum may, under some circumstances, play a more circumscribed role in response inhibition,

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whereas altered ventral striatum function might play a broader role in motivational processes.

## 4. Molecular Influences on Inhibitory Control

### 4.1. Dopamine

Medium spiny neurons of the striatum have canonically been divided into two populations: those of the striatonigral pathway that express dopamine D1 receptors and those of the striatopallidal pathway that express dopamine D2-like receptors (Gerfen et al., 1990). In line with imaging studies showing decreased striatal D2-like receptor availability in substance dependence, pharmacological and genetic studies have accentuated a role for striatopallidal neurons in inhibitory control. A study performed in our laboratory using primates showed that systemic administration of a D2/D3 receptor antagonist, but not of a D1/D5 receptor antagonist, was able to impair reversal learning performance (Lee et al., 2007). Similarly, in rodents, direct infusions of a D2-like receptor agonist into the nucleus accumbens, but not of a D1-like receptor agonist, also impaired reversal learning performance(Haluk and Floresco, 2009). Further, selectively blocking neurotransmission within the striatopallidal pathway, but not the striatonigal pathway, produced perseverative patterns of responding on the reversal learning task (Yawata et al., 2012). Lastly, mice with selective deletion of striatal adenosine 2A receptors, which are co-expressed with D2-like receptors, maintain goal-directed behavior following training procedures that produce habits in wild-type mice (Yu et al., 2009). These findings highlight a critical role of the striatopallidal pathway in rapid and adaptive shifts in behavior.

It is noteworthy that the contribution of D2-like receptors to inhibitory control is not specific to the reversal learning task, although the dissociation between D2- and D1- expressing neurons admittedly appears to be the most robust in this situation. For instance, striatal infusions of both D1/D5 and D2/D3 receptor antagonists are capable of altering stop signal reaction times, as well as premature responding on the 5-CSRT (Besson et al., 2010; Eagle et al., 2011).

The hypothesis that inhibitory control may be the causal construct through which alterations in striatal dopamine D2-like receptors influence addiction has been outlined above. Given this relationship, pharmacotherapies targeting this system may benefit treatment. That being said, there are a number of substantial issues that must first be addressed. First, while it is a predominantly consistent finding that drugs targeting D2-like receptors alter indices of inhibitory control, the direction of this relationship is sometimes ambiguous, with agonists and antagonists producing both decrements and enhancements in performance (Besson et al., 2010; Boulougouris et al., 2009; Ersche et al., 2011; Haluk and Floresco, 2009; Lee et al., 2007; Mehta et al., 2001). These discrepancies may be the consequence of dose-response functions, compound selectivity for dopamine receptor subtypes, and/or baseline differences in the number and/or distribution of receptors throughout the striatum. Understanding the dynamics by which the activation of receptor subtypes that have hitherto been confounded in drug studies (e.g. D2 and D3 receptors, D2 autoreceptors) interact with individual differences in these receptors must be more thoroughly explored. In addition, genetic and epidemiological studies identifying the source of variation in striatal D2-like receptors may

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provide predictors of drug response. Lastly, because D2-like receptor agonists have also been shown in animals to reinstate drug taking behaviors (Edwards et al., 2007; Self et al., 1996; Wise et al., 1990), the clinical benefits of enhancing inhibitory control must be weighed against the potential for increasing other processes that might promote recidivism.

Because of these issues, future research should address alternative means for modulating striatopallidal, D2-expressing medium spiny neurons. For example, research could address the interacting proteins that are co-expressed with dopamine D2-like receptors in discrete striatal cell populations to explore these possibilities; amongst the known interacting partners are adenosine A2A receptors and cannabinoid CB1 receptors (Ferre et al., 2009). Moreover, transcriptome profiling of D2-expressing neurons in the striatum have begun to generate lists of genes that are enriched in this cellular compartment, some of which have important actions on motivation and/or impulse control (Lobo et al., 2007; Lobo et al., 2006).

### 4.2. Serotonin

Though it is the focus of our review, dopamine is not unique in its modulation of inhibitory control; indeed, overwhelming evidence indicates that serotonin, acting on neurons of the orbitofrontal cortex, plays a major role in controlling inhibitory processes, with resulting effects of serotonin depletions and pharmacological manipulations on tasks that measure behavioral and response inhibition (Bari et al., 2009; Boulougouris et al., 2008; Brigman et al., 2010; Clarke et al., 2004; Clarke et al., 2005; Clarke et al., 2007; Eagle et al., 2009; Evenden, 1999; Izquierdo and Jentsch, 2012; Robbins and Roberts, 2007; Vallender et al., 2009). Though both dopamine and serotonin influence inhibitory control, it is not entirely clear if their effects are independent or interactive; some evidence supports the latter hypothesis. For example, the effects of serotonin depletion on impulsive behavior appear to depend, at least in part, upon dysregulated dopaminergic transmission (Winstanley et al., 2003; Winstanley et al., 2005). Moreover, we recently showed that individual differences in inhibitory control abilities in monkeys are explained by the interaction between cortical serotonin and striatal dopamine in a neurochemically and neuroanatomically specific manner (Groman et al., 2013). Though evidence for an interaction is therefore strengthening, the precise mechanistic account of this interaction remains to be delineated.

## 5. Inhibitory Control and Process Addictions

Mounting evidence suggests that inhibitory control deficits are not unique to addictions to drugs of abuse, but rather, may also play a role in process addictions, such as pathological gambling, compulsive overeating and/or sex addiction (Batterink et al., 2010; Blaszczynski et al., 1997; Cserjési et al., 2007; Jasinska et al., 2012; Leeman and Potenza, 2012; Steel and Blaszczynski, 1998; Verdejo-García et al., 2010; Vitaro et al., 1997). In light of the observation that inhibitory control deficits are found in these conditions, the question emerges as to whether their biological determinants are shared with drug addictions. Notably, people with morbid obesity exhibit, on average, lower striatal D2-like receptor availability, as well as decreased metabolic activity within the prefrontal cortex (Volkow et al., 2008; Wang et al., 2001). In addition, rats given extended exposure to high-sugar/fat foods reveal reduced D2 receptor protein in the striatum, and these changes are further

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associated with escalating body weight changes (Johnson and Kenny, 2010). Although these findings have not been causally linked to differences in inhibitory control, it is interesting to note that in one study, poor performance on the stop signal reaction time task was positively associated with the magnitude of obesity in children and was negatively associated with weight loss following behavioral treatment (Nederkoorn et al., 2007). Future experiments might directly examine the relationship between D2 receptors, inhibitory control, and treatment outcomes in obesity.

The relationship between pathological gambling and biological markers of inhibitory control is less consistent with that of substance dependence. For instance, although the propensity for gambling-like behavior in rodents has been associated with D2-like receptor availability (Cocker et al., 2012), a study of human pathological gamblers failed to find any group differences in striatal D2-like receptor availability (Clark et al., 2012). Nevertheless, pathological gamblers present altered activity in frontostriatal areas during a monetary delay task (Balodis et al., 2012), possibly suggesting that there are alternative aberrations in the inhibitory control circuitry. As more studies are conducted comparing the biological underpinnings of substance dependence with addictions not involving drugs of abuse, more will be able to be said about what the commonalities are, and further, what might distinguish between them.

## 6. Conclusions

Over the past dozen years or so, the concept that inhibitory control abilities are crucial to conceptual models of addiction has become well accepted in the field. Moreover, its relationship to addictions – both as a susceptibility factor and mediator of the progressive transition from use, to abuse, to dependence – has also been well established. Important roles of dopamine D2-like and serotonin receptors have also been delineated. Nevertheless, much work remains to be done. Only recently have genome-scale efforts begun to identify the genes that likely influence inhibitory control abilities in animal models (Laughlin et al., 2011), with similar efforts to identify novel loci for inhibitory control in humans as of yet not reported. The identification of neuropharmacological targets for medicines that reliably improve inhibitory control (Bari et al., 2009; Brigman et al., 2010; Floresco and Jentsch, 2011; Robinson et al., 2008; Seu and Jentsch, 2009; Seu et al., 2009) and potentially effectively suppress drug-taking behaviors is just beginning, and the value of already proposed molecules (e.g., atomoxetine) as candidate medications for addictions remains unclear. Finally, the value of biomarkers related to dopamine D2-like receptor function, either neuroimaging -based or proxy measures, in guiding intervention and prevention strategies has not been fully explored. Accordingly, the opportunities are many for deeper mechanistic and translational research into the molecular and systems neuroscience basis of inhibitory control problems in addiction.

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- The inability to effortfully inhibit drug-seeking and –taking actions is central to addictions.
- Impaired inhibitory control over motivated behaviors occurs as a consequence of drug experience.
- Natively poor inhibitory control abilities predict addiction susceptibility.
- Dopamine and serotonin, acting alone and in concert, influence inhibitory control.
- Improving inhibitory control may be an important new approach for treating addictions.

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## Table 1

Common Laboratory Measures of Inhibitory Control

| Procedure | Usual task setup | Test of inhibition | Species | Key References |
|---|---|---|---|---|
| *Stop signal reaction time task* | Choice reaction time procedure involving making speeded responses after presentation of a "go" cue (often visual) | On a minority of trials, a second stimulus is delivered after a response is initiated by the "go" cue. This is a "stop" command that instructs cancellation of the on-going response. | Rodents<br>Non-human primates<br>Human subjects | (Eagle et al., 2008; Godlove et al., 2011; Verbruggen and Logan, 2008) |
| *Go/No-go* | Simple reaction time task involving alternative presentations of a "go" cue or "no-go" cue. Subject responds rapidly only when the "go" cue is presented. | "No-go" cues are given infrequently, resulting in an overall pre-potent tendency to respond and a need to inhibit that on "no-go" trials. | Rodents<br>Non-human primates<br>Human subject | (Eagle et al., 2008; Iversen and Mishkin, 1970; Schoenbaum et al., 2002) |
| *Reversal learning* | Discriminated choice task involving trial-by-trial responses to concurrently presented stimuli. Each stimulus is differentially associated with reinforcing outcomes, and that which is most often associated with the largest size rewards tends to attract the most behavior. | Once the task is well learned, a switch in reinforcement contingencies is made. Stimuli initially reinforced at a high rate are now reinforced at a low rate, with the opposite occurring for stimuli initially reinforced at a low rate. Inhibition of the initially trained response must occur to enable new learning. | Rodents<br>Non-human primates<br>Human subjects | (Boulougouris et al., 2007; Clarke et al., 2007; Ersche et al., 2011a; Groman et al., 2011a; Izquierdo and Jentsch, 2012) |
| *Multiple choice (e.g., 5-choice) serial reaction time tasks* | Visual cues are presented in a temporally and/or spatially unpredictable manner, and a speeded response must be made in a manner congruent with the cue's instructional value (e.g., cues may instruct the spatial location of the correct response) | Responses made during the inter-cue intervals (before instructional cues are given) reflect inability to wait or to suppress pre-potent actions | Rodents<br>Human subjects | (Bari et al., 2008; Robbins, 2002) |