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Review

Impulsivity, Compulsivity, and Top-Down Cognitive Control

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Impulsivity is the tendency to act prematurely without foresight. Behavioral and neurobiological analysis of this construct, with evidence from both animal and human studies, defines several dissociable forms depending on distinct cortico-striatal substrates. One form of impulsivity depends on the temporal discounting of reward, another on motor or response disinhibition. Impulsivity is commonly associated with addiction to drugs from different pharmacological classes, but its causal role in human addiction is unclear. We characterize in neurobehavioral and neurochemical terms a rodent model of impulsivity based on premature responding in an attentional task. Evidence is surveyed that high impulsivity on this task precedes the escalation subsequently of cocaine self-administration behavior, and also a tendency toward compulsive cocaine-seeking and to relapse. These results indicate that the vulnerability to stimulant addiction may depend on an impulsivity endophenotype. Implications of these findings for the etiology, development, and treatment of drug addiction are considered.

Introduction

Impulsive behavior, for which a simple definition is the tendency to act prematurely without foresight, is associated with most forms of drug-taking, including alcoholism. It is often considered to be a product of impaired cognitive control and could potentially affect several aspects of the addictive process, including compulsive drug-seeking and relapse. A key question is therefore how such behavior causally contributes to aspects of drug addiction, as well as to other disorders of human decision-making. Surprisingly, this question has proven quite difficult to address. Although impulsivity may be a pre-existing personality trait, taking drugs may result in behavioral changes that include impulsivity, as a consequence of their pharmacological or "neurotoxic" actions in the brain.

The main goals of this review are to characterize the (multifaceted) nature of impulsivity (which involves various forms of response inhibition or "cognitive control"), to consider its significance in the causation of compulsive drug-seeking behavior (i.e., addiction), and to explore its neural mediation and origins. In particular, we will be addressing whether forms of impulsivity can be pre-existing biomarkers or "endophenotypes" for drug addiction.

The construct of impulsivity captures a set of behavioral characteristics that lay persons as well as clinicians can recognize as contributing to psychopathology. Of course, impulsive behavior is not always maladaptive; there will be occasions when it is advantageous to respond rapidly. As with many behavioral constructs, impulsivity is probably multifaceted, as can be gleaned from the following classic definition; "actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences" (Durana and Barnes, 1993). Deconstruction of this definition suggests that impulsivity could subsume behavior that has not adequately sampled sensory evidence ("reflection impulsivity"), a failure of motor inhibition ("impulsive action"), a tendency to accept small immediate or likely rewards versus large delayed or unlikely ones ("impulsive choice") and risky behavior, in the context of decision-making (see Evenden, 1999). Impulsivity can be also expressed in a number of different responses, including aggression. Given such a range of modes of expression of impulsivity, the question arises of whether we are dealing with a unitary construct. The evidence to be surveyed below using more operational measures of the impulsivity construct suggests that we are not and that it will eventually be necessary to formally define different forms of impulsivity; indeed, some progress toward that goal will be reported in this review.

Prototypical clinical disorders expressing impulsive behavior include attention deficit/hyperactivity disorder (ADHD), substance abuse and addiction, mania and antisocial behavior. There is probably some relationship (Hollander and Cohen, 1996), and often some confusion, between impulsivity and compulsivity. These two constructs have both been hypothesized to result from failures of response inhibition or "top-down" cognitive control. However, compulsivity can be captured by a modification of the definition of impulsivity: actions inappropriate to the situation which persist, have no obvious relationship to the overall goal and which often result in undesirable consequences. The argument will be made here therefore that compulsivity (which probably also comprises several distinct dimensions) and impulsivity may be distinguished by their involvement with different aspects of response control, presumably mediated by related, but distinct, neural circuitry linked with motivational and decisional processes. There is

considerable evidence that such circuitry includes the basal ganglia and their limbic cortical inputs, together with "top-down" control exerted by cortical, especially prefrontal, circuitry—modulated by neurochemical systems including the ascending monoaminergic projections to these terminal domains.

"Sensation-seeking" is also often bracketed with impulsivity (e.g., in the UPPS-Impulsive Behavior Scale [Cyders et al., 2009]) presumably because it frequently involves risky behavior, such as taking drugs or leaping from great heights; however, it does not necessarily entail a failure to inhibit prepotent responding and we will consider further the relationship of sensation-seeking to impulsivity below.

Measuring Impulsivity in Experimental Animals and Humans

Investigation of the neuropsychological basis of impulsivity has been greatly aided by the fact that, although there may be a variety of means for measuring impulsive behavior in human volunteers, many of these methods have analogs in animal behavior.

Delayed Discounting of Reward

Impulsive choice occurs when the individual preferentially chooses an immediately available small reward in preference to experiencing a delay for a larger one. Such choice can usually be characterized mathematically as hyperbolic discounting, which explains empirical findings originally in pigeons of "preference reversal"—the switch to choosing the smaller of the two rewards as their values decrease over time (Ainslie, 1975). In this sense, the animal and human paradigms may be quite comparable, in that they measure directly behavioral choice after relatively short temporal delays that are actually experienced by the subjects. However, many human versions of this paradigm, such as the Kirby test (Kirby and Petry, 2004), employ questionnaire-based methods in which subjects make subjective choices concerning imagined choices: e.g., would you prefer $100 after 2 days or $110 after 62 days? This type of test has been much used in the clinical domain for assessing impulsivity in psychiatric patients. A related paradigm is that of "probability discounting" of reward when the dimension of waiting is replaced by that of reinforcer uncertainty. Both forms of discounting behavior almost certainly contribute to performance on complex laboratory-based tests of decision-making such as the Iowa Gambling Task (Bechara, 2003), as well as to the everyday choices made by drug addicts or compulsive binge eaters as they accept short-term "highs" in preference to longer-term objectives such as good health. Impulsive choice is probably governed by a variety of factors that include decisions about relative value of rewards (e.g., as affected by delay and magnitude) and the ability to inhibit choices made to the more immediate options ("action restraint").

Motor Inhibition: Stop Signal Reaction Time

A very different form of impulsivity can be assessed by the ability to exert volitional control over a response that has already been initiated ("action cancellation") rather than in the choice selection phase. Failure to do so may result in an inappropriate, impulsive response, and this situation has been modeled in a test procedure called the "stop-signal reaction time task" (Logan, 1994) in which subjects are trained to respond as quickly as possible in a reaction time task. But on a proportion of trials, a "stop-signal" is sounded, which indicates that the subject has to cancel responding on that trial. Presentation of the stop-signal occurs at different time-points after the imperative signal, so it is much more difficult for subjects to cancel the response with increasing delay after the imperative signal than when the stop signal occurs immediately. The ability to stop behavior is measured by the stop-signal reaction time (SSRT), which can be inferred from a consideration of the response time distributions, and is based on a simple "race" model with "go" responses as measured by the "go" reaction time. This paradigm, originally conceived for use in humans, including patients with ADHD, can be implemented in rodents, for which strikingly similar estimates of SSRT can be obtained.

The SSRT task is a relatively sophisticated version of a classic neuropsychological task, the Go/NoGo procedure in which the subject has to choose between a stimulus associated with reward and another stimulus that cues inhibition of responding. In other words, the Go/NoGo task resembles the SSRT when the stop signal delay is 0 s. Although this appears to be a small procedural difference, Go/NoGo and SSRT performance can actually be affected differentially by the same manipulations, for example, those affecting serotonergic neurotransmission, which affect Go/NoGo choice, while having no effects on SSRT (Eagle et al., 2008a). This dissociation highlights how it is important to take into account the precise processes involved; Go/NoGo implicates response choice selection as well as action restraint, whereas SSRT involves the cancellation of an already selected response ("action cancellation"). Thus, response inhibition may clearly involve different subprocesses, depending on the precise programming of the action.

Premature Responding on the 5-Choice Serial Reaction Time Task

Another task that has been employed in rodents to measure impulsivity, in the context of general attentional abilities, is the 5-choice serial reaction time task (5CSRTT) (Robbins, 2002). This is based on a human test paradigm that is a forerunner of the well-known continuous performance task, employed for measuring sustained attention after drugs or stress or in clinical populations. In the rodent version, rats (or mice) are trained to detect brief visual targets to earn food. Anticipatory responses that occur prior to the onset of the visual signals are termed premature responses and are (usually) punished by time-out (darkness and reward delay). These "impulsive" responses contrast with the persistent, or perseverative, responses that sometimes occur in this test paradigm (and therefore are more accurately labeled as "compulsive responses"). The impulsive responses are more difficult to define in terms of the precise scheme laid out above; they arise as a consequence of the animal expecting a reward-related cue; however, they also evidently measure an aspect of response inhibition that is related to response selection in the Go/NoGo procedure. The impulsive responding is similar to that observed in so-called differential reinforcement of low rates of responding schedules, in which rats are trained to withhold responding for food until a set delay (often >15 s) has elapsed, except that the delays imposed before visual target presentation in the 5CSRTT are generally much

shorter and may depend to a lesser degree on the capacity for timing behavior. Nevertheless, in both of these cases, the response inhibitory process involved is action restraint during waiting for a reward. Thus, some overlap with delayed discounting paradigms is also evident, although these additionally depend on choice between the relative reinforcing value (or utility) of options (see above).

Self-Reported Impulsivity

In addition to these objective methods, impulsivity is generally assessed in humans using self-report as in the Barratt Impulsivity Scale (BIS-11), the UPPS-P Impulsive Behavior Scale (IBS), and the Kirby test of delayed discounting (see above). The BIS-11 comprises 30 items that are totaled to produce an overall score, with factor analysis having been employed to yield three major subscales: ''attentional,'' ''motor,'' and ''non-planning.'' Patton et al. reported high retest performance of the order of 0.8, for populations of substance abusers, prison inmates, general psychiatric patients, and undergraduates (Patton et al., 1995). The UPPS-P IBS is a 59 item self-report scale with five distinct subscales (positive urgency, negative urgency, lack of premeditation, lack of perseverance, and sensation-seeking) (Whiteside and Lynam, 2003). However, the subjective measurement of impulsivity often fails to bear a clear relationship with more objective methods, suggesting that they are assessing subtly different aspects; for example, self-report scales may reflect subjective commentary on impulsive-like behavioral output (Moeller et al., 2001).

Comparisons of Impulsivity Measures

More generally, correlations between performance on the various ''objective'' methods often also tend not to provide evidence of a unitary construct of impulsivity—for example, a multicenter study of ADHD found that SSRT and delayed discounting measures failed to correlate significantly, although together they defined the entire spectrum of ADHD disorder subtypes (Solanto et al., 2001). A study in rats examining various measures of impulsivity as affected by central 5-HT depletion also found little evidence of intercorrelation (Winstanley et al., 2004a). There are exceptions; for example, the steep discounting of delayed food rewards can predict aggression in rats (Van den Bergh et al., 2006). We will also be reporting evidence below that impulsivity as measured by the 5CSRTT and the delayed discounting paradigms share overlapping (but not identical) neural substrates. However, the general lack of intercorrelation means that, although the different tasks share some common features, such as the overall recruitment of inhibitory volitional control, this inhibition may be required at different points in the programming of response output (e.g., from choice, through response preparation to response initiation) and thus be implemented by different neural structures. This explains why impulsivity may be expressed at the behavioral level in different ways and why different measures of impulsivity may fail to intercorrelate.

The lack of intercorrelation between measures will thus inform our understanding of response control mechanisms in the brain, as well as sharpen the focus on which aspects of impulsivity provide the most predictive endophenotypes for psychiatric disorders. In fact, investigation of the neural substrates of impulsivity confirms that its different forms of expression are mediated by distinct, occasionally overlapping, neural systems.

Neural Substrates of Impulsivity

The neural substrates of impulsivity have mainly been studied in the context of response inhibition in humans as well as experimental animals. Although there has been a natural tendency to assume that inhibitory volitional control is exerted top-down by cortical mechanisms, implying that impulsivity could result from a relaxation of this control, there has been a growing appreciation that neural circuitry involving both cortical and subcortical mechanisms is implicated, particularly within the basal ganglia. Moreover, the possibility exists for impulsivity to be caused by chemical dysmodulation, not only of cortical processes but also at the level of the striatum (Figure 1).

Reward Discounting

In terms of impulsive choice, excitotoxic lesions of the nucleus accumbens core subregion produced remarkably potent shifts in choice for small, immediate food reward (Cardinal et al., 2001), a finding that has been replicated with different types of temporal discounting procedure in several other studies (Basar et al., 2010; Bezzina et al., 2007; Pothuizen et al., 2005). Pothuizen et al. also showed that similar lesions of the shell region of the nucleus accumbens were without effect (Pothuizen et al., 2005). The effects of nucleus accumbens core lesions on probability discounting are perhaps less well established, although there is some evidence for a preference for certain small rewards as distinct from uncertain larger ones (Basar et al., 2010).

The nucleus accumbens core region is also part of a larger neural network that includes the amygdala and the prefrontal cortex (Groenewegen et al., 1999). Accordingly, it is not surprising that lesions of the basolateral amygdala exert qualitatively similar effects on impulsive choice as accumbens core lesions (Winstanley et al., 2004b). For the orbitofrontal cortex, however, there is evidence of both steeper discounting (Mobini et al., 2002; Rudebeck et al., 2006) and the opposite tendency, a preference for larger, delayed reward (Winstanley et al., 2004b). There are several possible factors that may contribute to this: examining lesion effects during acquisition rather than established performance, including a reward-related stimulus (conditioned reinforcer) during the delay interval (Zeeb et al., 2010), and the possibility of opposed effects of lesions of the lateral versus the medial orbitofrontal cortex (Mar et al., 2008). This analysis is important because of the need ultimately to match these data to electrophysiological findings, for example in nonhuman primates (Wallis and Kennerley, 2010) and also the functional imaging of temporal discounting in human volunteers (Basar et al., 2010). The importance of the OFC in impulsive choice is supported by evidence showing enhanced release of dopamine from this region during the choice phase of delayed discounting (Winstanley et al., 2006b) and by molecular changes within the OFC, including ΔFosB during cocaine withdrawal-induced impulsive behavior (Winstanley et al., 2009).

There is some evidence from human functional imaging that separate neural systems mediate the selection of immediate and delayed options. Choice of either monetary reward or juice or water is consistently associated with increased activity of the ventral striatum and the medial PFC (Kable and Glimcher,

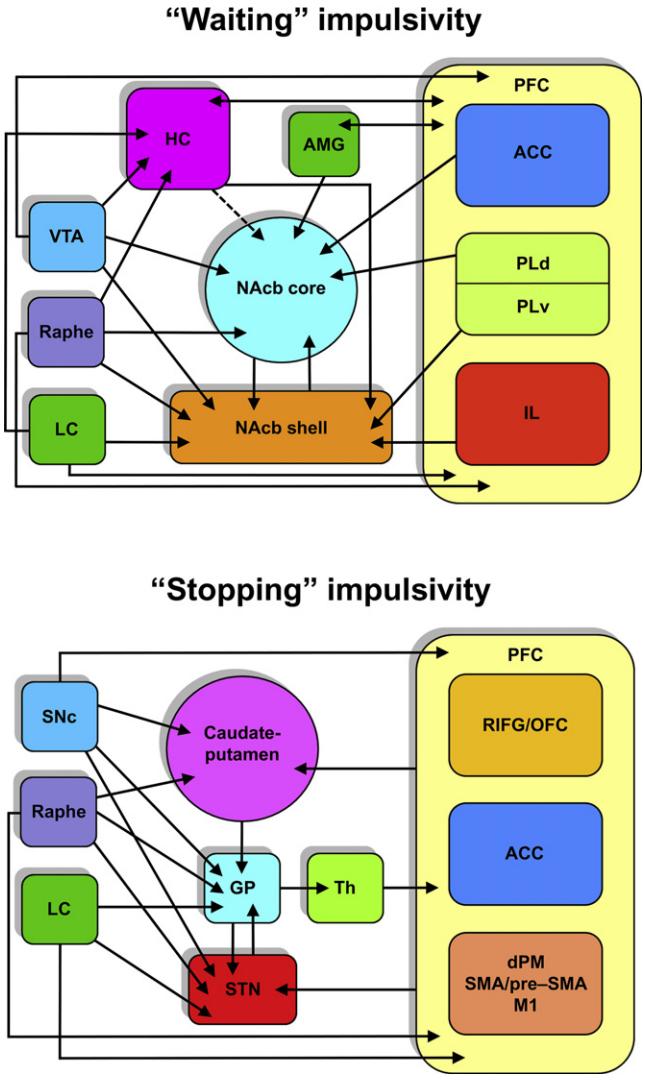

Figure 1. Schematic Representation of Neural Circuitry Mediating "Waiting" and "Stopping" Impulsivity

"Waiting impulsivity" depends upon top-down prefrontal cortical interactions with the hippocampus (HC), amygdala (AMG), and structures in the ventral striatum, including the nucleus accumbens core (NAcb core) and shell (NAcb shell). The anterior cingulate cortex (ACC), dorsal and ventral prelimbic cortex (PLd, PLv), and infralimbic cortex (IL) make distinct contributions to waiting impulsivity via topographically organized inputs to the NAcb. "Stopping impulsivity" depends upon neurally dissociable circuitry involving cortical motor areas (M1 primary motor cortex; SMA/pre-SMA supplementary motor area; dPM dorsal premotor area), right inferior frontal gyrus (RIFG), ACC, and the orbitofrontal cortex (OFC), as well as interactions with the dorsal striatum (caudate-putamen) and other basal ganglia structures, including the globus pallidus (GP) and subthalamic nucleus (STN), which project via the thalamus (Th) to the PFC. Both networks are modulated by midbrain dopaminergic neurons in the substantia nigra/ventral tegmental area (SNc/VTA), serotonergic neurons in the raphé nuclei (Raphe) and noradrenergic neurons in the locus coeruleus (LC). Note that intracortical connections are not shown. For clarity, neuromodulatory inputs to the AMG and Th are not shown. This figure was adapted, in part, from Chambers et al. (2009) with permission from Elsevier.

2009). Selections anticipating immediate reward disproportionately increased signal activity in the ventral striatum, medial prefrontal, and medial orbitofrontal cortices, proposed to represent an "impulsive" system. By contrast, choice of the delayed option was associated with higher activity in the lateral PFC and orbitofrontal cortex (Hariri et al., 2006; McClure et al., 2007), suggesting some form of balance between these systems, support for which has been noted in recent rodent studies (Mar et al., 2008). On the other hand, several studies have failed to confirm specifically increased ventral striatal activity during delayed discounting (Basar et al., 2010), and if this increase is to be linked with immediate choice, it may be difficult to reconcile with the rodent data showing that lesions of the ventral striatum (specifically, the nucleus accumbens core) actually have the same effect. However, one plausible interpretation of the fMRI data is that the signal observed within the ventral striatum during fMRI represents afferent input rather than output, and so the results of the excitotoxic lesions of the core region, which would selectively block its output, could be understood in these terms if such output inhibited choice of the immediate response option.

Go/NoGo and SSRT

Early work in nonhuman primates suggested that the lateral prefrontal cortex (PFC) had an especially important role in the control of Go/NoGo responding (Iversen and Mishkin, 1970), although the orbitofrontal cortex has also classically been related to disinhibition (Berlin et al., 2004). Subsequently, evidence from neuropsychological studies on brain-damaged patients, as well as functional imaging or electrophysiological studies in healthy volunteers or patients with attention deficit disorder, has suggested that the right inferior frontal gyrus (RIFG) may have an especially important role in top-down response control processes (Aron et al., 2003b).

Functional imaging studies defined a "stop circuit" in the SSRT task that included the RIFG, the anterior cingulate cortex, the presupplementary, and the motor cortex, as well as the basal ganglia, with a "hyperdirect" cortical projection to the subthalamic nucleus (Aron et al., 2007) (see Figure 1). This conclusion has been controversial (Aron, 2010), given that some studies indicate a role for left frontal cortex also, and others argue that the relevant activations are a product of attentional rather than inhibitory processes, a reasonable argument because the stopping response is a reaction to an external cue. However, it appears that Go/NoGo tasks more reliably activate the left frontal cortex than does the SSRT, possibly because of the additional response selection processes recruited (Rubia et al., 2001; see Eagle et al., 2008a). Aron (2010) reviewed evidence for functional dissociations within the RIFG region that correspond to attentional and response inhibitory zones, and Dodds et al. have explicitly contrasted attentional and response control functions associated with the posterior parietal cortex and RIFG, respectively (Dodds et al., 2010). Whatever the precise nature of the functions associated with the RIFG and its associated networks, it is evident that malfunction of this region is associated with impulsive behavior in healthy subjects and in ADHD (Casey et al., 2007). Moreover, the RIFG is associated with a modulation of the catecholaminergic enhancement of normal SSRT performance by atomoxetine (Chamberlain et al., 2009) and by methylphenidate and cocaine for the impaired performance of stimulant abusers (Garavan et al., 2008). The striatum is also implicated in impaired Go/NoGo performance in ADHD and its

remediation by methylphenidate (Vaidya et al., 2005), suggesting fronto-striatal interactions in behavioral control (Casey et al., 2007).

In general, the correspondence with animal studies has been encouraging. For example, it has recently been shown that the STN and the dorsomedial striatum (caudate) in rats have important roles in SSRT performance (Eagle et al., 2008b; Eagle and Robbins, 2003). However, it has proven to be more problematic in rats to identify the corresponding cortical control regions, doubtless because of problems of homology. In fact, lateral orbitofrontal damage selectively lengthens the SSRT, consistent with its projections to the dorsomedial striatum (Schilman et al., 2008). A significant dissociation has been revealed between the dorsal and ventral striatum, with excitotoxic lesions of the core subregion not affecting SSRT while exerting considerable effects on other measures of impulsivity, including responding under a differential reinforcement of low rates (DRL) of responding schedule and for delayed discounting (Eagle et al., 2008a).

5CSRTT and DRL Responding

The premature, anticipatory measure of impulsive behavior in the 5CSRTT has obvious similarities with DRL responding, in which waiting over a defined temporal interval is required for reinforcement, although the delays utilized in the 5CSRTT tend to be shorter (5–9 s versus, typically 20 s for the DRL 20 parameter). Lesion evidence suggests that the core region of the accumbens contributes to both DRL response inhibition and to premature responding on the 5CSRTT (Christakou et al., 2004; Pothuizen et al., 2005). Moreover, d-amphetamine administered either systemically or intra-accumbens increases premature responding on the 5CSRTT, an effect that is blocked by DA receptor blockade or DA depletion from the nucleus accumbens (Cole and Robbins, 1989; Pattij et al., 2007). The relative roles of the core and shell subregions have been highlighted by the findings of Murphy et al. (2008), who show that whereas core lesions enhanced impulsivity produced by systemic d-amphetamine (without in this case having any effect alone), shell lesions antagonized this increase. These observations are complemented by apparently opposed effects of deep brain stimulation (DBS) of these regions in rats, decreasing impulsivity in the shell but increasing it in the core (Sesia et al., 2008). These findings are compatible with the effects of the lesions if one assumes that the DBS enhances, rather than disrupts, the functioning of these nucleus accumbens structures. The clear involvement of the nucleus accumbens core in impulsivity both in delayed discounting and in terms of DRL and 5CSRTT performance is evident. However, it should be noted that its lack of involvement in stop-signal inhibition suggests that it does not participate directly in motor inhibition and provides compelling evidence against a simple ''motor inhibition'' hypothesis. However, the integrity of the nucleus accumbens is clearly necessary for preventing premature responding when anticipating or waiting for reward presentation.

Premature responses in the 5CSRTT are also under neurochemical modulation by other systems within the ventral striatum; although selective 5-HT depletion from this region fails to affect the measure (Fletcher et al., 2009), intra-accumbens 5-HT2A and 5-HT2C antagonists have opposite effects (blocking and increasing impulsivity, respectively) (Robinson et al., 2008a). Moreover, impulsivity on the 5CSRTT has been shown to be highly correlated negatively with measures of 5-HT turnover in the nucleus accumbens (Moreno et al., 2010). Noradrenergic mechanisms are also important, given that atomoxetine, the relatively selective noradrenaline transporter blocker, selectively reduces impulsivity in the 5CSRTT (Blondeau and Dellu-Hagedorn, 2007; Robinson et al., 2008b). In fact, atomoxetine reduces impulsive responding in the SSRT and delayed discounting paradigms also, suggesting some degree of commonality in their capacity to assess impulsive behavior (Robinson et al., 2008b)—although it is not necessarily the case that these effects are mediated by a common neural system, as opposed to diffuse effects of the ramifying central noradrenergic projections.

Although we are gradually building up a picture of how the nucleus accumbens is implicated in impulsive behavior (Basar et al., 2010), it is evident that there are also ''top-down''influences on this responding, from hippocampal and PFC afferents to the nucleus accumbens (see Figure 1) (Goto and Grace, 2008). For many years it has been known that hippocampal lesions induce premature responding on DRL schedules—a classic example of loss of ''behavioral inhibition'' (Gray and McNaughton, 1983). Moreover, there is burgeoning evidence of an involvement of the infralimbic (IL) PFC, the striatal projections of which are directed mainly to the shell subregion (Vertes, 2004). Thus, excitotoxic lesions of the IL-PFC, but not the more dorsal prelimbic (PL)-PFC, induce premature responding on the 5CSRTT (Chudasama et al., 2003); such an effect is also found after inactivation of the IL-PFC by infusing the broad spectrum NMDA receptor antagonist R-CPP (Murphy et al., 2005). Premature responding on the 5CSRTT can be blocked by intra-IL-PFC infusion of the 5HT2A receptor antagonist M100907 and the 5HT-1A receptor agonist 8-OHDPAT (Carli et al., 2006; Winstanley et al., 2003), probably because of the antagonism of glutamate release there (Calcagno et al., 2009). The elevated premature responding produced by intra-IL-PFC infusions of R-CPP is consistent with this hypothesis, given the elevation of extracellular glutamate resulting from such treatment (Calcagno et al., 2009; Carli et al., 2006).

The projections of the IL-PFC to the nucleus accumbens (Vertes, 2004) strongly indicate that the effects of manipulating the IL-PFC might be mediated by its top-down influence on mechanisms within the nucleus accumbens (Figure 1). However, there are other routes by which this influence may be exerted. Within the PFC, the IL-PFC projects only to the immediately proximal PL-PFC (Vertes, 2004), and other recent evidence is consistent with a role for this structure also (Hayton et al., 2010). Rats were trained in a simple response inhibition task to withhold responding until a signal was presented and synaptic plasticity of excitatory synapses in the mPFC was then measured with whole-cell patch-clamp recordings in brain slices prepared from trained rats. Response inhibition training significantly increased the relative contribution of AMPA receptors to the overall EPSC in PL, but not IL-PFC neurons of the medial PFC. This potentiation of synaptic transmission closely paralleled the acquisition and extinction of response inhibition. It was further shown that these plastic changes were selective for PL projections to the ventral striatum. It appears likely that

the PL-PFC plays an important role in response inhibition, perhaps both via its connections to the ventral striatum and also via its influence on motor cortex neuronal ensembles (Narayanan and Laubach, 2006).

An intriguing link to relapse in addiction is provided by parallel studies suggesting that exposure to drug-paired cues, after extinction of heroin self-administration, reduces the AMPA/NMDA ratio in the mPFC (Van den Oever et al., 2008) and thus promotes relapse to drug seeking. In line with these studies, inactivation of the dorsal mPFC blocks cue-, drug-, and stress-induced reinstatement of cocaine seeking after instrumental extinction (Kalivas and McFarland, 2003), and furthermore the consolidation of extinction of cocaine seeking behavior depends on glutamate transmission in the IL-PFC (LaLumiere et al., 2010). Thus, impulsive responding and relapse to drug seeking behavior may both result from failures in top-down PFC systems to regulate behavior at the level of the striatum.

Impulsivity and Drug Addiction

Impulsivity, in its multifaceted forms, is linked to addiction to drugs of several classes: stimulants, opiates, and alcohol (Perry and Carroll, 2008; Potenza and Taylor, 2009; Verdejo-García et al., 2008). With many of the classical methods for establishing impulsivity, including the BIS-11 and other scales, and in particular delayed discounting methods for monetary reinforcement, it has been well-established that steeper discounting is evident in opioid-dependent individuals (Kirby and Petry, 2004), heavy social drinkers (Vuchinich and Simpson, 1998), alcoholics (Petry, 2001), cocaine abusers (Kirby and Petry, 2004), methamphetamine abusers (Monterosso et al., 2007), and cigarette smokers (Bickel et al., 1999). There is also considerable evidence of impulsive responding with such tasks as the SSRT or Go/NoGo task in alcoholics (Noël et al., 2007), cocaine (Fillmore and Rush, 2002; Hester and Garavan, 2004), and methamphetamine (Monterosso et al., 2005) abusers. Methamphetamine abusers exhibit increased impulsivity as measured by the BIS-11 and also reduced DA D2/3 receptor binding in the striatum (Lee et al., 2009), the first such association to be shown in humans. Evidence of increased impulsivity is less clear in cannabis or MDMA abusers (Quednow et al., 2007).

Overall, it is evident that impulsivity, measured in a number of ways, is associated with some forms of drug abuse and seems likely to result from possibly multiple dysfunctions in cortico-striatal pathways associated with diverse forms of impulsivity. These dysfunctions may not always be caused by the same factors; some may be pre-existing and others drug-induced, both potentially coexisting in the same individual and contributing differentially to the addictive process.

Perry and Carroll (2008) consider the hypothesis that impulsive responding can be induced by drug-taking acutely and find only limited evidence for this possibility with delayed discounting procedures. Indeed, stimulant drugs are often found to reduce impulsive choice (both in humans and experimental animals). There is considerable evidence that alcohol increases impulsive responding in tasks such as Go/NoGo and the SSRT (de Wit, 2009). However, one recent study has shown that acutely administered cocaine can actually reduce deficits in a GoNo/Go procedure in cocaine-abusing humans, concomitant with a normalization of the BOLD response in the PFC (Garavan et al., 2008).

Although the evidence that acute administration of drugs of abuse induces impulsivity in humans is therefore slight, an alternative possibility, that chronic administration of such drugs causes neurotoxic effects on "top-down" control regions such as the PFC, is a viable alternative hypothesis (Everitt and Robbins, 2005; Jentsch and Taylor, 1999; Kalivas and Volkow, 2005)—although one that is much more difficult to test directly. There is little doubt that chronic drug abuse in humans is associated with substantial structural and metabolic changes in several cortical areas, including lateral PFC and the orbitofrontal cortex (Porrino et al., 2007; Robbins et al., 2008; Volkow et al., 2001). Moreover, it appears plausible that such changes enhance the transition to addiction, perhaps through relaxing control over subcortical mechanisms.

On the other hand, at least some of these apparent changes in brain function may actually reflect differences that were pre-existing prior to any drug abuse. How is it possible to untie this Gordian knot of cause and effect? Clearly, prospective studies of humans from an early age could in principle establish whether behavioral impulsivity and accompanying correlates of brain function antedate drug-taking and therefore could even be a risk factor for such drug taking. Such studies though rare indicate that impulsivity often precedes the onset of problem drinking and drug use (Nigg et al., 2006). The recent IMAGEN study of 2000 adolescents based in 9 European Centers hopes to obtain further prospective neurobehavioral indices of risk for future drug abuse by following this cohort carefully (Schumann et al., 2010). Another study has been able to predict the initiation of smoking behavior in adolescents at age 14 from delay-discounting measures at age 10 (Audrain-McGovern et al., 2009). A further strategy is to follow in epidemiological studies "at risk" groups, such as those adolescents with ADHD or children of drug addicts, many of whom will express behavioral impulsivity and associated brain changes (Verdejo-García et al., 2008).

Another, indirect method is to investigate impulsivity and other putative traits not only in drug addicts but also in their first-degree relatives, who are not abusing drugs. This classic approach to establishing endophenotypes (Gottesman and Gould, 2003) was recently implemented in a study by Ersche et al. (2010) that examined impulsivity and sensation seeking in a large group of stimulant abusers and their siblings, as well as age- and IQ-matched controls. As shown in Figure 2, impulsivity, but not sensation seeking, was significantly elevated in the siblings compared with controls, suggesting a possible inherited basis of impulsivity (there also being other possible causes), although sensation seeking was not significantly enhanced in this group. Of course, the drug users exhibited the highest levels of both sensation seeking and impulsivity, also supporting the likely conclusion that impulsivity may arise from a combination of predisposing and drug-induced effects—these are not mutually incompatible outcomes. On the other hand, sensation-seeking, although not predictive of future stimulant use, appears more specifically related to drug-induced rather than genetic effects.

The comparison of impulsivity and sensation-seeking was stimulated in part by animal studies (Belin et al., 2008) of what may be functionally equivalent tendencies in rats. In the

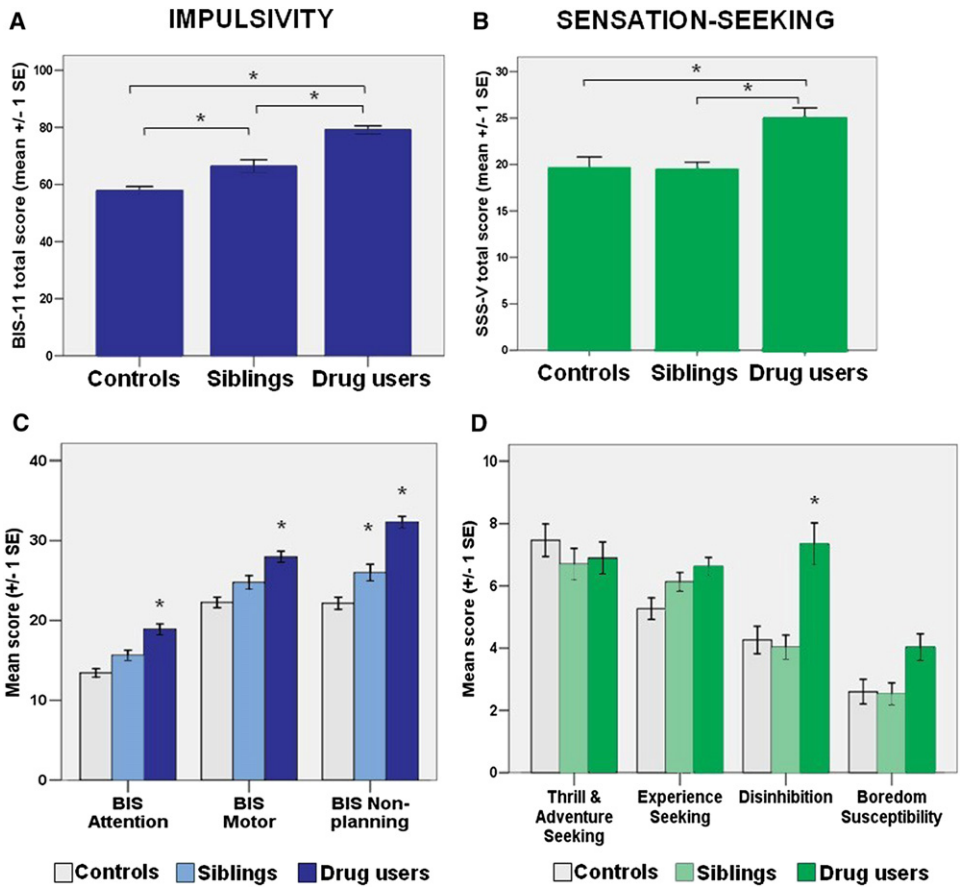

Figure 2. Endophenotypes of Drug Addiction

Self-reported levels of impulsivity and sensation-seeking in 30 sibling pairs of stimulant-dependent individuals and their biological brothers/sisters without a significant drug-taking history compared with 30 unrelated, non-drug-taking controls (A and C). Siblings reported significantly higher levels of trait impulsivity than the control volunteers but did not differ from controls with regard to sensation-seeking traits (B and D). Stimulant-dependent individuals reported significantly higher levels of impulsivity and sensation-seeking compared with both their siblings and controls. *$p < 0.05$ (versus controls). Data represent means ± SEM. This figure was reprinted from Ersche et al. (2010), with permission from Elsevier.

remainder of this article, we describe the approach of using animal experiments in which the genetic background and neurobehavioral phenotype of the animal can be characterized, prior to any controlled exposure to drugs of abuse.

Animal Models of Addiction Endophenotypes

Perhaps the earliest relevant study was the finding that rats preferentially (75% of trials) choosing small (two food pellets), immediate rewards over large (12 pellets) rewards delivered after a delay of 15 s subsequently consumed significantly more of a 12% alcohol solution than the less impulsive subgroups (Poulos et al., 1995). More recent studies extended the delayed discounting paradigm to cocaine self-administration, finding that "high impulsive" rats acquired cocaine self-administration more quickly than "low impulsive" rats (Perry and Carroll, 2008; Perry et al., 2005). These two studies clearly supported the hypothesis that high impulsivity, as measured by delayed discounting, is a vulnerability factor for both alcohol and cocaine self-administration. A third set of studies had shown that rhesus monkeys subjected to social stress as adolescents consistently self-administered intravenously more cocaine than nonstressed animals and additionally showed lower levels of dopamine (DA) D2/3 receptor binding in the striatum (Morgan et al., 2002). This result was very significant given the studies by Volkow and colleagues showing that chronic cocaine, methamphetamine, and alcohol abusers had reduced DA D2/3 receptors in the striatum and, furthermore, that that non-drug-abusing volunteers had a greater "liking" for i.v. methylphenidate when they exhibited relatively lower D2/3 striatal receptor binding potentials—given that they indicate possible pre-existing changes in D2/3 receptors prior to drug exposure (Volkow et al., 2002; Volkow et al., 1993; Volkow et al., 1999; Volkow and Wise, 2005). Initial studies by the Nader group on rhesus monkeys did not characterize in detail the behavioral phenotype associated with their findings of reduced striatal D2/3 receptor binding. However, it has subsequently emerged that the dominant (high striatal D2/3 receptor availability) monkeys are slower to contact a novel object, consistent with them being novelty-reactive and the low D2/3 receptor availability monkeys having faster latencies and thus potentially exhibiting impulsive behavior (Czoty et al., 2010).

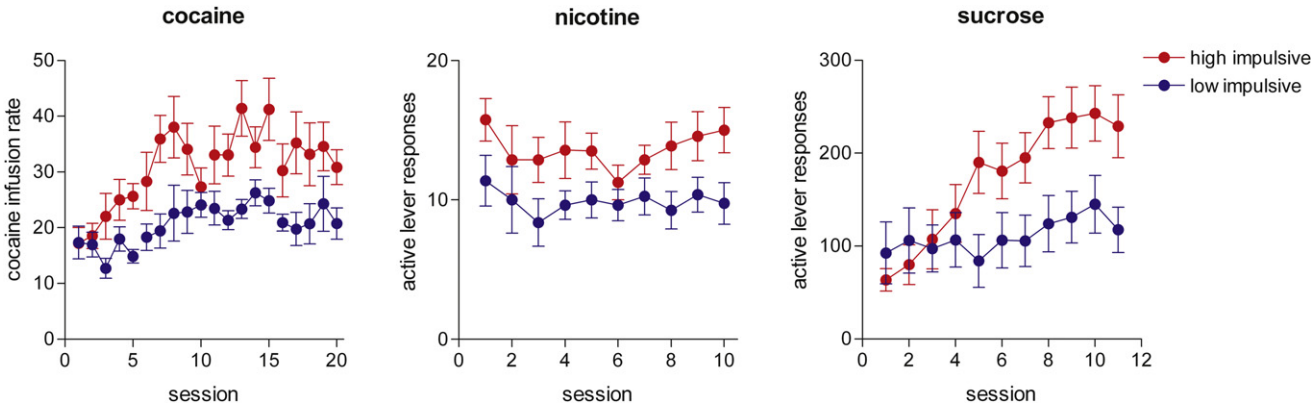

Figure 3. Rats Selected for High Impulsivity on the 5CSRTT Show Enhanced Self-administration of Cocaine, Nicotine, and Sucrose Compared with Low-Impulsive Rats

Data from Dalley et al. (2007) (cocaine; reprinted with permission from AAAS), Diergaarde et al. (2008) (nicotine; reprinted with permission from Elsevier), and Diergaarde et al. (2009) (sucrose; use of APA information does not imply endorsement by APA). Data represent means ± SEM.

Recognizing that self-administration per se may not be the most sensitive indicator of the tendency to addiction, Dalley et al. (2007) took a different approach by investigating the propensity to escalate cocaine i.v. self-administration as an index of the addictive potential of cocaine (Ahmed and Koob, 1999). They also used the criterion of excessive impulsive responding in the 5CSRTT to identify impulsivity, given that previous findings (Dalley et al., 2002) had indicated a bimodal distribution of impulsive responding in the Lister hooded strain of rats, according to this measure. In the previous study, changes in serotonin levels within the PFC had been identified in the high impulsive rats, together with evidence of enhanced DA turnover in the anterior cingulate cortex.

An additional finding in the 2007 study was that the high impulsive rats had reduced DA D2/3 receptor binding in the ventral, but not the dorsal striatum. Furthermore, this reduced level of binding significantly correlated with the level of impulsive behavior in the 5CSRTT, a correlation that is strikingly parallel to that seen in human methamphetamine abusers (Lee et al., 2009). Dalley et al. (2007) showed that high-impulsive rats greatly escalated, or lost control over, their cocaine intake compared to low impulsives, but were no different in their initial acquisition of self-administration (Figure 3).

These findings, while again supporting the concept of a neurobehavioral endophenotype that predicts vulnerability to drug (in this case, cocaine) abuse, of course raises many issues. Are similar relationships evident for other drugs of abuse? How precisely defined is the behavioral endophenoptype? For example, is the construct of impulsivity the most appropriate? Which neural circuitry is implicated? How do these neurobehavioral changes arise, are they the product of genetic or epigenetic factors? Significant advances can be reported for many of these questions, below.

Extension to Other Drugs of Abuse and Reinforcers. A similar measure of impulsive responding on the 5CSRTT was found to predict enhanced nicotine self-administration and enhanced resistance to extinction (see Figure 3) (Diergaarde et al., 2008), thus extending the link with impulsivity to the more general class of stimulant drugs. However, these high impulsive rats were not apparently more susceptible to cue-induced reinstatement of nicotine seeking behavior. These findings contrasted slightly with those obtained when rats were screened for high impulsivity alternatively using the delayed discounting procedure, but these rats were also more susceptible to nicotine in other ways.

Inactivation of the medial raphé nucleus by muscimol infusions was shown to increase premature responding on the 5CSRTT and also to reinstate alcohol seeking (Lê et al., 2008), but whether high-impulsive rats would exhibit greater ethanol consumption is yet to be established. One clear negative is that high-impulsive rats screened on the 5CSRTT do not exhibit enhanced acquisition or escalation of i.v. heroin self-administration (McNamara et al., 2010). The latter result is of interest, given the evidence that both heroin addicts (Kirby and Petry, 2004) and rats treated with opiates (Pattij et al., 2009) exhibit evidence of enhanced impulsivity, as defined by effects on delayed discounting of reward.

Refining the behavioral phenotype. An obvious question is whether the findings for impulsivity defined according to the 5CSRTT and delayed discounting paradigms are comparable—whether they both measure a unitary construct of impulsivity. The findings of Diergaarde et al. (2008) suggest that the 5CSRTT and delayed discounting tasks are measuring something in common that we can perhaps label as a "waiting impulsivity" that is related to vulnerability to nicotine reinforcement. This suggests mediation by overlapping neural substrates, although the subtly different relationships with susceptibility to nicotine suggest some differences also.

The most direct comparisons have been to compare high- and low-impulsive rats on the 5CSRTT in other settings designed to assess impulsivity. For example, high-impulsive rats on the 5CSRTT also exhibited significantly steeper discounting functions, consistent with the unitary construct of "waiting impulsivity" suggested above (Robinson et al., 2009). However, it was significant that the high-impulsive rats did not show impaired (i.e., slower) SSRTs, suggesting that there is a dissociation between "failing to wait" and "failing to stop" forms of

impulsive behavior, perhaps reflecting distinct neural substrates (e.g., ventral versus dorsal striatum, see above and Figure 1). As we have seen above, both forms of impulsivity may be impaired in chronic stimulant abusers, but our evidence in rats suggests that the "failing to stop" impulsivity, though often associated with stimulant abuse (e.g., Fillmore and Rush, 2002), may not be an endophenotype for cocaine addiction, although this remains to be tested in both rats and humans.

Impulsivity has frequently been associated with sensation seeking and so may be linked to the processing of novelty. An early, seminal study (Piazza et al., 1989) reported that high reactivity to novelty (presumably as a consequence of increased anxiety) predicted faster acquisition of i.v. self-administration of d-amphetamine and so the issue arises of whether the high-impulsive rats were similarly novelty reactive. The high-reactive rats were defined as such by their increased levels of locomotor activity in novel circular corridors. However, we could find no evidence of increased locomotor activity in photocell activity cages in our high-impulsive 5CSRTT animals (Dalley et al., 2007), suggesting that reactivity to novelty is not core to the impulsivity construct.

A later study (Belin et al., 2008) explicitly classified the same population of rats as high versus low impulsive or as high versus low novelty reactive on the basis of their locomotor activity scores. The findings were very revealing. The high-reactive rats were indeed more sensitive to cocaine and acquired i.v. self-administration more rapidly. However, the high-impulsive rats did not acquire cocaine self-administration more rapidly, but did exhibit greater evidence of compulsive cocaine-seeking behavior by tolerating mild foot-shock punishment readily in a cocaine-seeking paradigm (Belin et al., 2008). Moreover, the high-impulsive rats were more prone to relapse to cocaine seeking after punishment-induced abstinence (Economidou et al., 2009).

These striking results indicate that the two endophenotypes, novelty reactivity and impulsivity, may contribute to different phases of cocaine self-administration, for example, initiation and persistence—we consider the latter to be more predictive of addiction potential. The data also underline the considerable individual differences that underlie the drive to addiction and the fact that only a proportion of animals subjected to drug exposure actually become "drug-addicted" in the operational sense (Deroche-Gamonet et al., 2004; Pelloux et al., 2007). The results indicate that impulsivity as defined by premature responding is not equivalent to the greater responsivity of rats shown to novel situations. The findings may also bear on the possible relationship of impulsivity to compulsivity; it is notable that Roman High Avoidance rats exhibit not only evidence of impulsivity on the 5CSRTT and delayed discounting but also elevated schedule-induced polydipsia, a possible model of obsessive-compulsive disorder (Moreno et al., 2010).

However, other possible phenotypes should be considered; novelty reactivity is not the same as novelty preference, and impulsivity may also be associated with diminished anxiety. Recent studies (Molander et al., 2011) show that there are small, significant correlations of 5CSRTT impulsivity with measures of novelty preference and diminished anxiety as measured by entries into the open, elevated arm of a Y maze. However, these are minor and could well be explained by the response disinhibition that underlies all of the measures. Interpretation of a recent correlation of enhanced novelty preference with measures of compulsive cocaine seeking is therefore somewhat compromised by the lack of any concurrent measure of impulsivity (Belin et al., 2011).

High impulsivity on the 5CSRTT does not seem simply to be a consequence of altered timing (Mar et al., 2009) or impaired stimulus control; attentional measures on the 5CSRTT are often unaffected in high-impulsive rats, although there may be a small decrement in accuracy, possibly relevant to an ADHD phenotype (Dalley et al., 2007). There is evidence that high-impulsive rats more readily respond for high-incentive foods such as sucrose (see Figure 3) (Diergaarde et al., 2009). However, motivational factors do not appear primary; although 5CSRTT impulsivity can be reduced by satiety (Robbins, 2002), the latencies to collect earned rewards are no faster than in low-impulsive rats (Dalley et al., 2007). A suggestion that impulsivity might be related to an increased propensity to approach Pavlovian cues predicting food was also not supported (Robinson et al., 2009). Finally, and perhaps most significantly, although high levels of impulsivity could in theory arise because of slowed learning to negative feedback (and in that sense be an example of perseverative or compulsive behavior, as distinct from impulsivity), in fact, high-impulsive rats eliminate their impulsive behavior at a similar rate to low-impulsive animals during the course of a session with long intertrial intervals that normally elevate premature responding in both low and high impulsives (Mar et al., 2009). Overall, the evidence indicates that the high-impulsive behavior on the 5CSRTT is a relatively well-defined example of response inhibitory failure associated with reward anticipation produced by lengthy delays to reinforcement, rather than being secondary to a phenotype related to anxiety or reactivity to novelty.

Implications

Toward a Possible Neural Endophenotype for Impulsivity

The definition of neural circuitry that contributes to impulsivity, in its multifaceted forms, is an obvious objective in the search for endophenotypes. It is entirely possible that superficially similar behavioral syndromes arise from differences in the ways that distinct components of this putative circuit operate. Whether it is one in particular or several of these different behavioral neuro-endophenotypes that best predict vulnerability to cocaine also remains to be seen. A summary of the present circuitry putatively associated with 5CSRTT impulsivity based on the evidence reviewed in "Neural Substrates of Impulsivity" is shown in Figure 1. Major elements are the core and shell subregions of the nucleus accumbens, possibly in a functionally opposed manner (Murphy et al., 2008), the infralimbic and prelimbic cortices, as well as the anterior cingulate cortex and hippocampus having apparently "top-down," response inhibitory roles. The possible role of the orbitofrontal cortex is less clear; it has been implicated occasionally in impulsive responding but also in measures of perseveration (possibly reflecting "compulsivity") in this task (Chudasama et al., 2003). Clearly, there are several ways by which top-down control may be implemented: from the ll-PFC or the hippocampus to the shell, from the

PL-PFC to the core and by currently unspecified interactions between the core and shell regions, either directly or indirectly via "spiralling cascades" of striato-VTA-striatal circuitry (Haber et al., 2000). Indirect evidence for "top-down" control over striatal functioning is provided by the finding that increased impulsive responding produced by medial PFC lesions is alleviated by intra-accumbens infusions of the D2/3 receptor antagonist sulpiride (Pezze et al., 2009).

Regulation of inhibitory responding by neuromodulation may occur from the noradrenergic locus coeruleus (to the shell region) and from the midbrain dopamine and dorsal raphé serotonin systems. Early studies of amphetamine-induced impulsive responding in the 5CSRTT suggested that high levels of presynaptic DA might be responsible: depletion of DA from the nucleus accumbens by 6-OHDA blocked amphetamine-induced increases in premature responding (Cole and Robbins, 1989). Such increases were boosted by core, but reduced by shell, lesions (Murphy et al., 2008). Additionally, amphetamine-induced increases were blocked by infusion of a D2/3 receptor antagonist into the core region (Pattij et al., 2007). These findings complement those of Besson et al. (2010) showing that the preferential D3 receptor antagonist nafodotride significantly reduced impulsive responding in 5CSRTT impulsive rats when infused intracore, but enhanced it intrashell, apparently consistent with the observed reductions of D2/3 receptors in the ventral striatum found in such animals (Dalley et al., 2007).

These findings of apparently altered DA receptor function call into question the status of presynaptic DA activity in high-impulsive rats. For example, a reduced D2/3 binding potential might have arisen from displacement by elevated DA release. However, there were no obvious baseline differences in DA activity in the ventral striatum of 5CSRTT high-impulsive rats, as indexed by microdialysis. Moreno et al. (2010) also found no relationship between impulsivity in the 5CSRTT and measures of presynaptic DA function in the nucleus accumbens. Thus, although it is the case that amphetamine undoubtedly increases premature responding on the standard version of the 5CSRTT paradigm as a consequence of elevated DA release, and this is also consistent with evidence from human PET studies that impulsivity is correlated with reduced D2 autoreceptors and increased displacement of DA by methylphenidate (Buckholtz et al., 2010), this may not be the case for the 5CSRTT high-impulsive rat. Other investigations are to some extent equivocal: thus in vitro measures of DA release were higher in the shell region of 5CSRTT impulsive rats, compared to controls, but lower in the core subregion; on the other hand, both regions showed reductions in DA release in rats exhibiting impulsive choice (Diergaarde et al., 2008). The latter finding may be consistent with the results of Moreno et al. (2010) showing that high DA levels in the nucleus accumbens correlated significantly with choices for a large reward.

Furthermore, there are other addiction phenotypes not based on impulsivity; thus the "high reactive" rats studied by Flagel et al. (2010) had increased DA "transients" in the core region and increased binding of high-affinity DA D2 receptors. Clearly, the precise ways in which accumbens DA is regulated could be crucial in determining not only the behavioral phenotype, but also its precise relevance to cocaine susceptibility. An alternative interpretation of the reduced D2/3 binding of the 5CSRTT impulsive rats is in terms of phenotypic and/or structural changes in medium spiny neurons bearing D2 receptors. This possibility has recently been highlighted by structural magnetic resonance imaging of high-impulsive rats that has revealed apparent reductions of gray matter in the core region (as well as in frontoparietal areas) compared with controls (Caprioli et al., 2010). This observation is consistent with those showing that core lesions can result in increased impulsivity, although this may depend on the precise behavioral context (Cardinal et al., 2001; Christakou et al., 2004; Pothuizen et al., 2005). An additional possibility is that this phenotype is also associated with reduced top-down control over striatal subregions. It is evident that further refinement of these measures will enable the definition of the neural circuitry associated with the high impulsive syndrome, and these measures will also provide a potential "biomarker" for the impulsive behavioral trait. Whether such neural (and their accompanying behavioral) changes are actually caused solely by genetic factors is yet to be tested; evidence already points to the possibility that certain environmental factors influence D2/3 receptor function and thereby susceptibility to cocaine taking (Nader et al., 2008).

A Neurogenetic Perspective on Impulsivity

There is considerable evidence for heritability in drug addiction (Kreek et al., 2005; Uhl, 2006), but a large number of genes have been implicated for many different pharmacological classes of drugs of abuse that transcend the molecular differences in modes of action that characterize these drugs. Perhaps key to such analyses however are the underlying endophenotypes, whether they are impulsivity, risk taking, sensation seeking, anxiety, sensitivity to drug reinforcement, or some other trait. Kreek et al. provide an informative table that illustrates the cross-involvement of such traits with candidate genes. Notably, impulsivity (obviously defined in several ways) has been linked with several genes regulating dopaminergic and serotoninergic function: the DRD4, DAT, TRP1 (tryptophan hydroxylase), SERT, MAOA, and COMT, as well as those affecting GABA-ergic function (GABRA1 and GABRA6). Another recent addition is the serotonin 2B receptor (Bevilacqua et al., 2010). Hamidovic et al. (2009) additionally describe data linking impulsive behavior in humans to polymorphisms of the DA D2 receptor. It should be emphasized that the array of genes is likely to have wide-ranging and even independent effects on impulsivity and cognitive control, especially given their different distributions in the brain and the multifaceted nature of these constructs (and hence phenotypes).

An alternative approach to identifying relevant genes may be to pursue a behavioral genetic approach combined with genome-wide scanning. Two recent studies have shown the utility of this approach. Moreno et al. (2010) utilized the Roman High and Low Avoidance rat strains, with the High Avoidance animals being more impulsive. In rats bred for high (HR) and low (LR) novelty reactivity, the HR rats approach cues associated with food or cocaine more readily than LR rats (Flagel et al., 2010). However, although this would perhaps be consistent with an impulsive phenotype, these rats also displayed less "impulsive choice" and therefore can be differentiated from the 5CSRTT high impulsives who also failed to exhibit heightened "autoshaping" to food-predictive cues (Robinson et al., 2009).

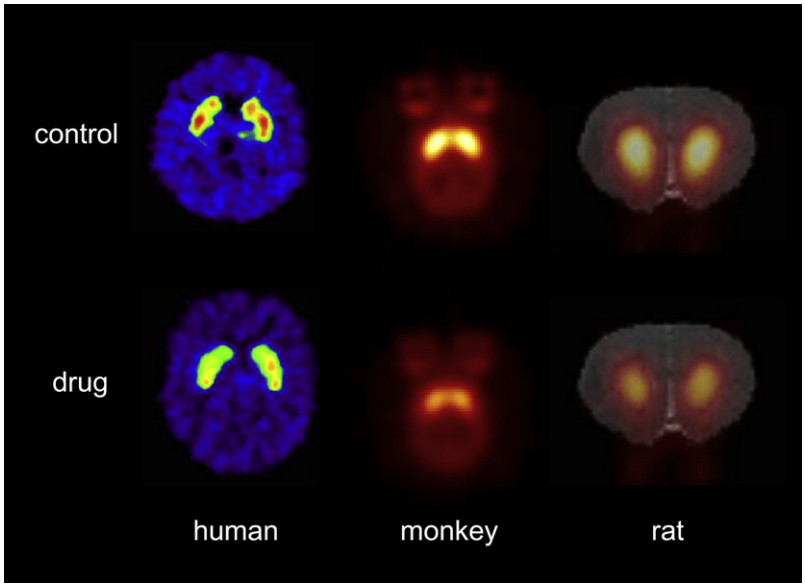

Figure 4. Positron Emission Tomography Scans
Positron emission tomography scans showing reduced dopamine D2/3 receptor availability in the striatum of a recently abstinent cocaine addict (reprinted from Volkow et al., 2002, with permission from Elsevier), a rhesus macaque monkey exposed to 3 months intravenous cocaine self-administration (reprinted from Nader et al., 2006, with permission from Macmillan Publishers Ltd.) and a Lister-hooded rat exposed to intravenous amphetamine self-administration (reprinted from Dalley et al., 2009, with permission from Elsevier).

A different genetic strategy is to compare a large number of recombinant mouse strains and attempt to define the quantitative trait loci associated with impulsivity. This approach has been initiated with studies of the C57BL/6J and DBA2/J mice, which have relatively high and low levels of impulsive responding on the 5CSRTT, respectively (Pena-Oliver et al., 2010). The notion that C57BL/6J mice are particularly impulsive is given further credence by the finding of rapid discounting functions in this strain after delayed reinforcement (Isles et al., 2004).

In summary, several strategies are being pursued currently in the search of genes related to the impulsivity phenotype in human and rodent studies, and we can expect further candidates to emerge in the next period, although the interactive role of environmental factors has also to be explored.

Implications for Understanding Addiction

Self-medication. The fact that impulsivity is actually often reduced by stimulant drugs, whether administered clinically to patients with ADHD (Aron et al., 2003a) or experimental animals (Winstanley et al., 2006a) including self-administration (Dalley et al., 2007), suggests that the drug regulates or remediates, in some sense, the neural substrate responsible for the hyperimpulsivity. The fact that impulsivity predicts subsequent cocaine intake is therefore also consistent with the hypothesis that the impulsive rat's self-administration behavior represents some form of "self-medication," especially as the hyperimpulsivity is actually reduced to control levels during the period of self-administration (Dalley et al., 2007). Although it seems unlikely such behavior reflects some conscious appraisal of a deficient central state that the rat seeks voluntarily to reverse, it is possible that, at least initially, the reinforcing value of the drug is sensed in terms of an adaptive change in central state. However, should the behavior develop "binge" and habitual qualities it seems likely that neurotoxic effects may overwhelm any apparently beneficial effects on response inhibitory control. Moreover, although stimulants such as cocaine, which are preferentially taken in the presence of low D2/3 striatal receptors, may also in parallel restore a normal level of DA function, it should be noted that evidence indicates that further stimulant drug taking actually downregulates striatal D2/3 receptors (see Figure 4) (Dalley et al., 2009; Nader et al., 2006) so that if the self-administration behavior is conceived as a form of "self-medication," in the long term it may serve only to "make the problem worse," hence placing the stimulant drug abuser in a cycle of chronic drug abuse.

Relationship of Impulsivity to Compulsivity. Previously, it has been suggested that there are habitual qualities to drug taking, which place much more emphasis on drug-related external stimuli and their response eliciting capabilities, than on any notional hypothesis that the drug taking persists because of its enduring incentive properties (Everitt and Robbins, 2005). The fact that high-impulsive rats come to exhibit compulsive cocaine-seeking behavior (they persist in seeking and taking cocaine despite punishment of seeking responses) supports the link between a putative trait of impulsivity and the addictive process. The hypothesis thus emerges that impulsivity may be a causal factor for addiction, rather than being simply associated with it. One way to test this hypothesis would be to block impulsive responding and its development (e.g., with a putative medication) and observe whether this is sufficient to prevent compulsive drug seeking and taking. Indeed, the anti-impulsive medication atomoxetine prevents the greater propensity to relapse seen in high impulsive rats in abstinence (Economidou et al., 2009). It remains a possibility that it would not, in which case the likely association between impulsivity and stimulant drug abuse may arise from a third, shared but undefined, factor. Another, indirect test of the hypothesis, is to determine whether high impulsivity also predicts a predilection toward impairments in proxy measures of compulsive behavior, such as perseveration during reversal learning, even without any experience of self-administering the drug. Such a relationship between impulsivity and compulsivity may then possibly reflect the operations of similar underpinning neurobehavioral processes such as top-down inhibitory control.

Conclusions

The "impulsivity" construct has been a useful heuristic, capturing some aspects of a neurobehavioral state that may predispose toward addictive behavior in humans, as well as in

other animals. Our current analysis predicts that what is generally denoted as impulsivity will be fractionated into distinct forms that may, however, often coexist in the same individual. These forms arise from a dysfunctioning of fronto-striatal circuitries in a spectrum-like manner to reveal several manifestations of disrupted top-down cognitive control. Some of the key questions remaining are the origins, genetic and otherwise, of "impulsivity traits" as well as the necessary and sufficient conditions that lead from impulsive syndromes to compulsive behavior.

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