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Dissecting impulsivity and its relationships to drug addictions

J. David Jentsch,[1] James R. Ashenhurst,[2,*] M. Catalina Cervantes,[1,*] Stephanie M. Groman,[1,*] Alexander S. James,[1,*] and Zachary T. Pennington[1,*]

[1]Department of Psychology, University of California Los Angeles, Los Angeles, California. [2]Interdepartmental Neuroscience Program, University of California Los Angeles, Los Angeles, California

Address for correspondence: J. David Jentsch, Department of Psychology, University of California Los Angeles, Box 951563, Los Angeles, CA 90095-1563. jentsch@psych.ucla.edu

Addictions are often characterized as forms of impulsive behavior. That said, it is often noted that impulsivity is a multidimensional construct, spanning several psychological domains. This review describes the relationship between varieties of impulsivity and addiction-related behaviors, the nature of the causal relationship between the two, and the underlying neurobiological mechanisms that promote impulsive behaviors. We conclude that the available data strongly support the notion that impulsivity is both a risk factor for, and a consequence of, drug and alcohol consumption. While the evidence indicating that subtypes of impulsive behavior are uniquely informative—either biologically or with respect to their relationships to addictions—is convincing, multiple lines of study link distinct subtypes of impulsivity to low dopamine D2 receptor function and perturbed serotonergic transmission, revealing shared mechanisms between the subtypes. Therefore, a common biological framework involving monoaminergic transmitters in key frontostriatal circuits may link multiple forms of impulsivity to drug self-administration and addiction-related behaviors. Further dissection of these relationships is needed before the next phase of genetic and genomic discovery will be able to reveal the biological sources of the vulnerability for addiction indexed by impulsivity.

Keywords: inhibition; decision making; vulnerability

Impulsivity

Impulses are strong motivational urges to engage in reward pursuit or consumption and can lead to *impulsive behaviors*, unless individuals effortfully inhibit or interrupt them.[1,2] *Impulsivity* refers to a trait-like proclivity to engage in these behaviors, either due to unusually strong impulses or to difficulty with reasoning about or controlling impulsive actions.

Impulsive behaviors are not necessarily pathological and likely reflect the individual's desire/motivation to obtain high-salience outcomes like social dominance,[3] high-energy nutrients,[4] sex,[5–7] or other rewards. They are, in that sense, adaptive behaviors that may well have been subject to selection forces that encourage quick exploratory or risk-taking actions in favor of slower, more deliberative and risk-averse choices. The advantageous nature of a certain degree of impulsive tendency is likely reflected in the fact that alleles associated with higher propensity for impulsivity are highly conserved in mammals; for example, the dopamine D4 receptor exon 3 variable number tandem repeat polymorphism is often linked with impulsive behaviors in humans,[8–10] nonhuman primates,[11–13] and dogs.[14,15]

These behaviors are viewed as pathological when they become intrusive, disrupt normal life routines, cause clinical distress, or lead to harmful consequences for oneself or others,[16] possibly at the point where there is a failure in the inhibitory self-control mechanisms that are called upon to interrupt or suppress these behaviors.[1,17,18]

*These authors contributed equally to the preparation of this manuscript and are listed in alphabetical order.

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Pathological impulsive behaviors are either diagnostic or common sequelae of a range of psychiatric disorders, including the so-called impulse control disorders, attention deficit/hyperactivity and conduct disorders,[19–24] bipolar (manic-depressive) disorder,[25] borderline personality disorder,[26,27] and (of most relevance to this review) substance-use disorders.[22,23,28–33] Impulsivity also appears to be a significant major contributor to suicidality in patients with these disorders.[34]

The relationship of impulsivity to each of these disorders is clinically meaningful (e.g., impulsive behaviors are per se symptoms and directly contribute to psychological distress), but the fact that it features in each of these conditions may be more than simply descriptive. Indeed, these disorders are a constellation of syndromes that are frequently comorbid with one another, and one hypothesis is that a heightened impulsive tendency is a common influence driving the simultaneous presentation of these conditions.[21,30,35–43]

Impulsivity versus compulsivity

Pathological, intrusive behaviors that present in mental disorders can be viewed, alternatively, as being strongly driven by motivational urges to obtain a desired outcome (impulsive) or as repetitive, automatic, and outcome-independent actions (compulsive); this distinction roughly maps on to the dissociations between goal-directed and habit-like behavior.[44] Because the neural mechanisms that contribute to goal-directed and habitual actions are separable,[44,45] the view that a clinically impairing behavior in a particular disorder is one or the other is potentially meaningful in terms of underlying pathophysiology. To some degree, many of the problematic behaviors in mental disorders in general, and in substance use disorders in particular, can arguably be viewed as impulsive or compulsive—or perhaps reflecting a transition from heightened impulsivity to heightened compulsivity.[30,31,46,47]

As noted above, pathological impulsive behaviors may evolve in some, or even many, cases from an erosion of inhibitory, self-control abilities, and this is almost certainly true for compulsive actions as well. Compulsive behaviors are not necessarily pathological themselves; rather, it is progressive loss of control over habits that defines a pathological course. In that sense, the window into inhibitory control abilities we get from the study of impulsivity and impulse control almost certainly also generalizes in many cases to compulsive behaviors.

Impulsivity and drug addictions

The role for impulsivity in the initiation, maintenance, and relapsing nature of drug-seeking and drug-taking behaviors, and in clinically impairing drug use disorders, has only received attention comparatively recently.[1,23,29,30,33,42] Though impulsivity is not directly named as a symptom of substance use disorders in the rubric of the Diagnostic and Statistical Manual of the American Psychiatric Association,[48] the concept of impaired control over impulsive or compulsive drug use features prominently.[47] Additionally, a considerable amount of theory suggests that—even if impulsivity is not itself a key feature of end-stage addiction—it likely contributes substantially to the progression toward it.

Impulsivity and/or poor impulse control could have an influence on almost all stages of the life cycle of drug use. Theoretically, they could be linked with heightened probability of initiating drug use, of rapidly escalating drug use, of failing to cut down on drug use once it becomes problematic, and of relapsing despite motivation to remain abstinent.[22,23,28–31,33,42,47,49–54] These contributions can be better understood through a deeper examination of the causal relationships between impulsivity, drug use, and addiction; for example, whether impulsive tendencies pre-date the onset of drug use behaviors or whether experience with drug use causes or exacerbates the propensity for impulsivity. These directional linkages will be a major topic of this review.

Forms of impulsivity

Before further detailing the relationships between impulsivity and addictions, it is crucial to note that there exist many conceptually and procedurally distinct measures of impulsivity and impulsive behaviors (Table 1). In a highly influential article, Evenden[2] details the different theoretical approaches to measuring impulsivity, which have long held that impulsivity and impulsive behavior are not singular phenomena. The reasoning for a multifactorial model of impulsivity starts with its descriptions and definitions. Beginning with the attempts of psychometricians and personality theorists to understand impulsive tendencies (or related

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Table 1. Hypothetical dimensions of impulsivity and associated specific tasks and measures that have been commonly used in research program of multiple labs

Domain	Construct	Specific forms	Tasks	Measures	Key reference(s)
Impulsive action	Inhibitory response control	Action inhibition	Stop-signal reaction time task (rats or humans),	Stop-signal reaction time (individual estimate of time between go and stop cues that supports predetermined rate of successful stopping); longer stop-signal reaction times = worse action inhibition	18 18 31
			go/no-go task (rats or humans),	Percent of commission errors (responding on no-go trials); higher error rates = worse action inhibition	
			reversal learning (rats or humans)	Number of trials required before choice accuracy meets criterion after reversal of contingencies or proportion of erroneous responses to initially trained stimulus after reversal; more trials before reaching criterion performance or more errors post-reversal = poorer action inhibition	
		Waiting	5CSRTT (rats or humans) DRL (rats)	Number of target responses made before cues are presented; higher number of premature responses = difficulty waiting Number of trials in which a response is made before the waiting interval elapses; higher number of trials with early responses = difficult waiting	60 61
Impulsive choice	Decision making	Sensitivity of choices to delay	Delay discounting tasks; adjusting amounts (rats or humans)	Preference for a larger, delayed (versus a smaller, immediate) reward as a function of the delay to its delivery after a choice is made; individual estimates of negative rate of change of preference as delay increases are reflected in modeled variable: K; larger K values = greater impulsive choice	182
		Sensitivity of choices to risk	Iowa gambling task (rats or humans)	Preference for net suboptimal high-gain/high-loss response options over net optimal low-gain/low-loss options; greater relative preference for high-gain/high-loss options = more impulsive style of decision making	228,244
			Probability discounting task (rats)	Preference for a larger versus smaller reward as a function of the probability that the large reward will not be delivered; greater preference for certain, relative to uncertain, rewards = more impulsive style of decision making	254
			Balloon analogue risk task (humans and rats)	Propensity to engage in serial responding to increase reward accumulation, despite an underlying accruing risk of reward forfeiture; greater average reward pursuit/risk acceptance per trial = more impulsive style of decision making	224,225

phenomena) and extending into the descriptions of clinically impairing impulsivity,[48] there is substantial variability in the characteristics that are viewed as indicators of it and in the forms in which it manifests. Many of these concepts and definitions were embedded into implementations of laboratory tasks that were designed to operationally measure forms of impulsive behavior (Table 1). One example is the divide between impulsive behavior that seems to reflect compromised ability to inhibit inappropriate behaviors (impulsive action) and a tendency to make choices leading to suboptimal immediate or unduly risky outcomes (impulsive choices),[20,32,55] as demonstrated in Table 1.[20,32,55]

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In the following sections, we will discuss the empirical data linking various forms of impulsive behavior, measured in humans and laboratory animals, to drug seeking and drug taking. Our focus is on those measures of impulsivity whose relationships to addiction have been studied sufficiently, including impulsive action, waiting behavior, and delay- and risk-related decision making. We will then turn to the neural circuitry and pharmacological mechanisms that underpin these forms of impulsive behavior. Our discussion is guided by our view that, if these manifestations of impulsive behavior are distinct psychological processes, they should relate to addiction-related behaviors in different ways; additionally, they should rely upon substantially nonoverlapping neural circuitries and depend upon separable molecular and pharmacological substrates. In his review, Evenden drew upon his own very comprehensive set of behavioral pharmacological studies, arguing that varieties of impulsive behavior can sometimes show different responses to various drug manipulations.[2] This review adds to the discussion by addressing whether unique neural mechanisms predict individual variation in subtypes of impulsivity and whether these varieties of impulsivity exhibit distinct relationships to addiction behaviors.

Inhibitory response control

Inhibitory response control is a cognitive mechanism that enables effortful, goal-directed suppression of motor responses. As noted above, this includes exerting control over both goal-directed, reward-seeking (impulsive), and automatic and/or habitual (compulsive) actions. In either case, failures of inhibitory control can result in hasty actions made with little forethought of the consequences of the behaviors. The proposed significance of inhibitory response control to drug addiction, in particular, is that impairments in this domain might figure centrally into the compromised ability to control drug seeking and taking.[1,31,33,56–58]

Conventional tests of inhibitory response control

A number of tests are commonly used in the laboratory to measure inhibitory response control in animals and humans (Table 1). This discussion cannot be comprehensive; rather, it will focus on the tasks most commonly used in the field. These include tests of action inhibition and procedures that emphasize waiting or delaying reward-seeking responses. The following section provides a description of each task and commentary on the advantages/disadvantages of each, as well as on the translational value of the measures.

Action inhibition tests. In stop-signal and go/no-go tasks, subjects are required to make frequent, speeded motor responses to a "go" signal. On a smaller subset of trials, subjects are presented with a "stop" signal, and failures to suppress responding are measured. One key difference between stop-signal and go/no-go tasks is the time at which the stop signal is presented.[18] In go/no-go tasks, stop signals are either presented in combination or in lieu of the go signal; conversely, in the stop-signal task, stop signals are presented after the go signal is presented, such that subjects must stop and/or inhibit an already initiated response. By parametrically varying the time between the presentation of the go and stop cues, one can create a quantitative, individualized estimate of the time required to inhibit an ongoing response, referred to as the individual's stop-signal reaction time.[59] Both procedures have been used extensively in both human and animal research.[18]

Procedures involving reversal learning can also index the ability of subjects to selectively withhold conditioned responses during learning.[31] These tasks usually consist of a phase in which subjects are trained on a set of stimulus–outcome or response–outcome associations. After the initial association is learned, the trained contingencies are unexpectedly changed or reversed and subjects must then learn to selectively inhibit the previously reinforced response in order to avoid punishment and/or obtain reward. High rates of responding to the originally trained association are considered to be one index of impulsive (or perhaps compulsive) action.

The adaptability of the reversal-learning paradigm has facilitated its use in a variety of species.[31] Species-appropriate learning protocols can be used, each configured with a reversal problem and need for response inhibition, making reversal learning one of the more useful measures of inhibitory response control available to translational behavioral neuroscience research.

Tests of waiting. Tasks such as the 5-choice serial reaction time test (5CSRTT)[60] and differential

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reinforcement of low rates of responding (DRL) schedules[61] have been used to measure the ability to withhold behavior while waiting for the opportunity to obtain a reward. The 5CSRTT, commonly considered the rodent analog of a human continuous performance task, was designed to measure attentional ability by requiring rodents to make spatially congruent responses following presentation of a brief visual stimulus. However, responses made at inappropriate times, most notably premature responses made during the intertrial interval, have been proposed to index difficulty with waiting, a form of impulsive responding.[60]

DRL schedules have been used in rodents to measure the ability to wait to make an action (as opposed to the ability to wait for reinforcement following a choice, as in delay discounting: see below); in these procedures, appetitive reinforcement occurs only if a response is made after a certain, relatively long interval of time has passed.[61] Waiting impulsivity is assessed by how frequently early responses are made, and in consequence, how many rewards are forfeited.

While similar in some respects, the forms of waiting impulsivity described here (namely, premature responses in the 5CSRTT and reinforcement rate in the DRL) are differentiated from the measure of waiting behavior captured by delay discounting tasks (Table 1). The former are more highly intertwined with action inhibition—that is, withholding an often reinforced behavior until it is appropriate to emit the behavior—while the latter emphasizes a decision-making process, whereby subjects weigh the merits of a smaller, immediate reward versus a larger, delayed reward, but not inhibition of responses themselves.

Relationship to impulsive temperament

Laboratory measures of inhibitory response control (Table 1) are meant to provide an objective, quantitative measure of variation in impulsivity; here we describe the relationship between response inhibition laboratory tasks and self-reported impulsivity, as indexed by personality scales.

Action inhibition tests. The impulsivity subscale of the Eysenck Personality Inventory has been associated with stop-signal reaction time scores,[62] as have parent/teacher reports of externalizing behaviors in children.[63] A weak correlation has been observed between go/no-go performance and Barratt Impulsiveness Scale scores, with no such correlation observed with stop-signal inhibition.[64] Studies comparing the performance of individuals in reversal-learning tasks with self-reported levels of impulsivity have indicated that difficulty reversing discrimination problems is associated with heightened levels of self-reported levels of impulsivity.[65] Together, these data suggest that the laboratory tasks of action inhibition measure, at least partially, the same forms of impulsivity measured with personality scales.

Relationship to substance use disorders

The following section deals with the observed relationship between measures of inhibitory response control and drug self-administration in animal models or with subclinical or clinical substance use in humans.

Action inhibition tests. Individuals affected by substance use disorders have been repeatedly shown to exhibit impaired stop-signal inhibition,[66–68] as well as deficits in go/no-go performance.[69,70] These impairments appear to be both an antecedent risk factor for and consequence of drug use. Unaffected relatives of substance-dependent probands display longer stop-signal reaction times,[68,71] suggesting that impaired response inhibition measured using this task is a preexisting heritable endophenotype for addictions. Conversely, a history of cocaine self-administration is sufficient to elicit deficits in stop-signal performance in monkeys.[72]

In human subjects, reversal-learning performance is impaired in some substance-dependent individuals.[73–75] These effects appear to result, at least in part, from chronic exposure to drugs of abuse, because animal models exposed to drugs of abuse in either experimenter-delivered or self-administration paradigms exhibit reversal-learning problems as a consequence.[76–78] On the other hand, a recent study demonstrated that inbred strains of mice previously shown to exhibit difficulty inhibiting a response during reversal learning[79] also showed a greater propensity to self-administer cocaine, as compared to strains with relatively normal or good reversal-learning abilities.[80]

Results from a variety of tests therefore suggest that the relationship between impairments in action inhibition and addiction-related behaviors run in both directions in a causal fashion, with poor inhibition predicting heightened propensity to

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self-administer drugs and with drug experience causing an erosion of inhibitory abilities. What remains unknown, to some extent, is whether subjects differ in the direction or magnitude of drug-induced changes in action inhibition as a function of their baseline competency, as well as whether this relationship holds for all drugs of abuse (the data gathered so far have mostly involved the study of stimulants).

Tests of waiting. Waiting to respond also appears to be impaired in substance use disorders, whether one uses 5CSRTT variants[81] or DRL tests.[82] These deficits may well proceed the onset of drug use because the 5CSRTT can be used to identify a pattern of waiting impulsivity—present in a minority of rats—that predicts an elevated propensity to self-administer cocaine or nicotine,[83,84] but not heroin,[83,85] and with enhanced susceptibility for the development of a compulsive pattern of cocaine seeking.[85] Finally, impulsive responding in the 5CSRTT predicts escalation of sucrose intake and susceptibility to cue-induced reinstatement of sucrose seeking, pointing to its ability to predict a dyscontrolled, hyperactive reward-seeking and reward-taking phenotype that extends beyond drugs of abuse.[86] By contrast, neither amphetamine,[87] heroin, or cocaine self-administration,[88] even when coupled with repeated withdrawal episodes, produces lasting changes in premature responding in the 5CSRTT at the group level in rats; strikingly, when analyses are focused only on rats with pre-existing high impulsivity in the 5CSRTT, cocaine self-administration experience actually lessens waiting impulsivity.[89]

While the predictive value of DRL for self-administration is unknown, repeated, intermittent (experimenter-delivered) administration of cocaine, nicotine, methamphetamine, or amphetamine is sufficient to impair waiting in this test,[90–93] even when withdrawal periods are imposed in between the final drug administration and test.[94]

Though 5CSRTT and DRL are viewed from the perspective that they both measure waiting, it is clear that their individual relationships to addiction-like behaviors are different. Waiting in the 5CSRTT predicts self-administration behaviors (much like tests of action inhibition do), but drug experience does not impair waiting in this task at the group level (and, indeed, reduces it in rats with baseline high impulsivity). Waiting in the DRL, on the other hand, is highly sensitive to drug experience. This suggests that, even within one domain of inhibitory response control, different tests exhibit unique relationships to addiction-related behaviors.

Neural circuitry of inhibitory response control

Inhibitory response control is often linked with the integrity of brain systems interconnecting regions of the frontal lobe and basal ganglia. In the following section, we will refer to both lesion and imaging data in animals and humans that help to illuminate the specifics of these anatomy–behavior relationships. In particular, the similarities and differences between the underlying neural circuits responsible for inhibitory control performance in different tasks can help to address the question of whether there is a common biological pathway to impulsive action or whether this phenotype is itself heterogeneously determined and multidimensional. A summary of the experimental studies in rodent models (demonstrating cause–effect relationships) are depicted in Figure 1.

Action inhibition. Functional neuroimaging studies have repeatedly implicated a circuit comprising ventral parts of the frontal lobe and the basal ganglia in the stop-signal task.[24] Neuropsychological studies of brain-damaged patients have revealed an important contribution of the right inferior frontal gyrus, in particular, to stop-signal performance.[95] In the case of rodent models, lesions of the rodent orbitofrontal cortex,[96] but not of the medial prefrontal cortex (PFC),[96,97] and the medial[98] but not ventral[97] striatum, have been found to slow stop-signal reaction times (Fig. 1). It has been proposed that the right inferior frontal gyrus exerts top-down influence over striatal regions, possibly via the subthalamic nucleus,[99] to mediate response inhibition within the stop-signal task. A very similar pattern of results is found for go/no-go tasks.[100–102]

The neural mechanisms that govern action inhibition during reversal learning are remarkably similar, if not identical, across species.[31] Areas within the corticostriatal circuit that include the orbital regions of the frontal cortex and the dorsomedial striatum have been identified as being necessary for optimal inhibitory control during reversal-learning tasks.[31] Functional MRI studies have also provided support for this hypothesis.[103,104]

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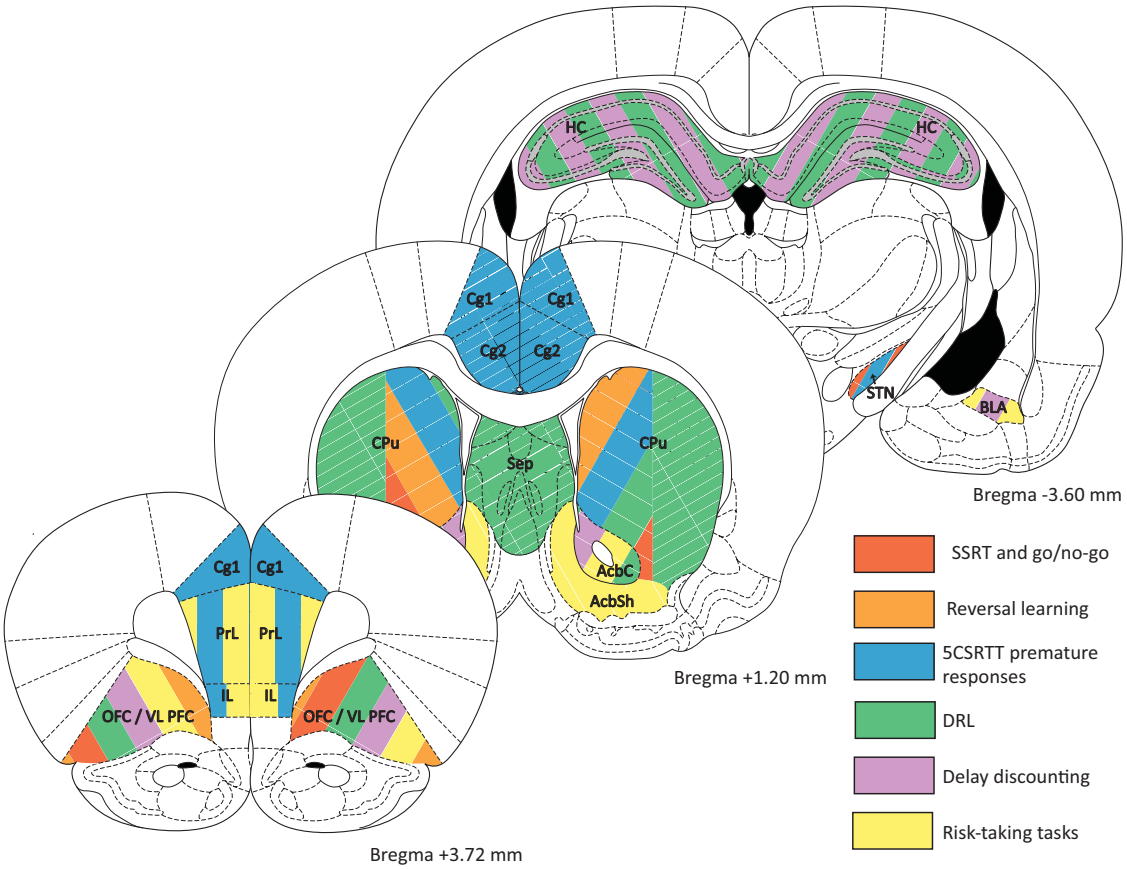

Figure 1. Anatomical localization of brain regions involved in inhibitory response control or delay- or risk-related decision making. This figure is color coded according to regions implicated in various laboratory measures of inhibitory response control. Cg1/Cg2, Zilles' areas for anterior cingulate cortex; PrL, prelimbic cortex; IL, infralimbic cortex; OFC/VLPFC, orbitofrontal cortex/ventrolateral prefrontal cortex; Sep, septal nuclei; CPu, caudate/putamen nucleus; AcbC, nucleus accumbens core; AcbSh, nucleus accumbens shell; HC, hippocampus; STN, subthalamic nucleus.

Collectively, these data support the notion that an at least partially overlapping circuit involving lateral inferior portions of the frontal lobe and dorsomedial parts of the striatum is implicated in various forms of action inhibition.

Tests of waiting. The neural circuitry underlying waiting includes the medial, but not orbital, regions of the frontal cortex (Fig. 1), as lesions of the infralimbic and anterior cingulate cortices increase premature responding in the 5CSRTT, while damage to the orbitofrontal, parietal, and lateral frontal cortices do not.[105–107] Moreover, lesions of the medial and lateral striatum, but not the ventral striatum, increase premature responding in the 5CSRTT.[108,109] Like stop-signal performance, effective inhibition of anticipatory responding in the 5CSRTT also involves the subthalamic nucleus.[110]

Waiting in the DRL task is not as sensitive to removal of the medial PFC.[111,112] Instead, it appears to depend upon a circuit encompassing ventrolateral frontal regions, the caudate/putamen, nucleus accumbens core, and the septohippocampal system.[111,113–115]

From the perspective of brain regions necessary for performance, the tests of waiting again show a discrepancy, with 5CSRTT depending on medial and DRL depending upon ventrolateral frontal cortices. Notably, waiting in the 5CSRTT is linked mechanistically with frontal cortical subregions that are distinct from tests of action inhibition (Fig. 1).

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Table 2. Effects of pharmacological manipulations of monoaminergic signaling on inhibitory response control

				Serotonin		Dopamine	Norepinephrine
		Depletion	Reuptake inhibition	-2A antagonist	-2C antagonist	D2 antagonist	Reuptake inhibition
Action inhibition	Stop-signal reaction time task	No change	No change	Not done	Not done	↑	↓
	Reversal learning	↑	↓	↑	↑	↑	↓
Waiting	5CSRTT	↑	↓	↓	↓	Variable	↓
	DRL	↑	↓	↓	Not done	Not done	↓
Delay-related decision making	Delay discounting	↑	↓	Not done	Not done	Variable	↓
Risk-related decision making	Gambling tests	↑	No change	Not done	Not done	Variable	No change

Upward arrows indicate that the manipulation increased impulsive responding in the test, while downward arrows indicate a reduction in impulsive responding in the test. Effects are drawn from studies cited in the text.

Pharmacological regulation of inhibitory response control

The following section addresses the question of whether the set of neurotransmitters and/or molecularly defined neurotransmitter receptor subtypes necessary for various forms of action inhibition and waiting are similar or distinct. As noted above, one key argument in favor of the delineation of these forms of impulsivity from one another has been their differential sensitivity to pharmacological manipulation of monoaminergic systems.[2,55,116] The following section will focus on monoamine systems, at the expense of discussing other relevant systems, such as glutamate, GABA, acetylcholine, and cannabinoids, because the majority of research in the field has focused on monoamine systems, allowing for a more comprehensive, comparative analysis of different forms of inhibitory response control. The pattern of results discussed below is graphically displayed in Table 2.

Serotonin and action inhibition

Although depletion of forebrain serotonin levels—presumably impairing serotonergic transmission—has repeatedly been shown to affect go/no-go performance[117] and reversal learning,[118–121] serotonin appears to play little role in inhibition in the stop-signal task.[122–124]

Elevations in brain serotonin, caused by genetic or pharmacological interference with the serotonin transporter, enhance reversal-learning performance,[125–128] and variation in the serotonin transporter gene influences inhibitory control during reversal learning in monkeys.[129,130] At least with respect to reversal learning, antagonism of serotonin-2C receptor enhances the ability of rats to learn a spatial reversal task,[131,132] an effect mediated by the orbitofrontal cortex,[133] while blockade of serotonin-2A receptors impairs reversal performance.[131]

Serotonin and waiting

The literature linking serotonergic transmission to waiting is extensive. With respect to the 5CSRTT, genetic or pharmacological disruption of the serotonin transporter or administration of agents that elevate synaptic serotonin levels reduce premature responding,[128,134,135] while depletion of brain serotonin has the opposite effect.[116,136,137] Activation of serotonin-1A receptors[137] or blockade of serotonin-2C receptors increases premature responding, while serotonin-2C agonists or serotonin-2A antagonists

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(the latter given systemically or into the PFC) decrease premature responding,[138–140] again supporting an oppositional relationship between serotonin-2A and -2C subtypes (albeit the direction of the relationships appears to be opposite to those described for reversal learning and DRL performance).

Waiting in DRL tests is impaired by serotonin depletion[141] and is improved by manipulations that elevate serotonergic transmission.[61] Systemic administration of serotonin-1A agonists and serotonin-2 antagonists improve waiting in DRL schedules.[142,143] The role for subtypes of serotonin-2 receptors is complex, with systemic activation of serotonin-2C receptors or antagonism of serotonin-2A receptors improving waiting.[144,145] This opposing influence of serotonin-2C and 2A receptors on DRL performance is similar to that observed for 5CSRTT.[131]

Dopamine and action inhibition

Dopaminergic mechanisms play a role in all forms of action inhibition. For example, response inhibition in the stop-signal task is impaired after pharmacological blockade of dorsomedial striatal dopamine D2-like receptors, while D1-like receptor blockade in the same brain region increases inhibition in this task.[146] Further supporting these results, D2-like receptor stimulation improves stop-signal inhibition in humans,[147] and individual differences in striatal dopamine D2-like receptor availability, measured with positron emission tomography (PET), vary negatively with the stop-signal reaction times.[148]

Similar results are found for reversal learning. Genetic or pharmacological interference with dopamine D2-like, but not D1-like, receptors impairs inhibition during reversal learning[31,149–151] (but see Ref. 152), and individual differences in D2-like receptor expression/availability within the striatum positively correlate with reversal-learning performance competency in mice and monkeys.[79,153] Finally, variation in the *DRD2* gene is linked with reversal-learning abilities in humans.[154] Overall, these data strongly support the notion that dopaminergic transmission at D2 receptors promotes action inhibition in a confluence of laboratory tests. Given that reductions in striatal D2-like receptor availability have been repeatedly found in individuals with substance-use disorders,[155] these findings are of particular clinical interest.

Emerging evidence suggests that the serotonergic and dopaminergic influences on action inhibition in the reversal-learning task are mechanistically linked. Specifically, we found a relationship between individual differences in the ability to inhibit inappropriate responses in a reversal-learning test, and analysis of brain monoamine transmission in monkeys identified a statistical interaction between levels of serotonin in the orbitofrontal cortex and dopamine in the dorsal striatum that predicted action inhibition.[156] These data indicate that serotonin and dopamine interact to influence response inhibition, rather than simply acting as two distinct and orthogonal influences.

Dopamine and waiting

Dopamine likely exerts complex effects on waiting in the 5CSRTT. For example, within the medial PFC, activation of D1-like receptors leads to reduced anticipatory responding,[157] while depletion of dopamine in the ventral striatum decreases, and systemic or local application of amphetamine increases, this behavior.[158,159] Additionally, heightened anticipatory responding has been associated with low dopamine content and reduced dopamine D2-like receptor availability in the ventral striatum.[83,160] Pharmacological manipulation of D2-like receptors affects this form of impulsivity and its modulation by amphetamine,[159,161] with baseline impulsivity affecting sensitivity to D2 manipulations.[162] Moreover, the core and shell subregions of the nucleus accumbens may exert opposing influences on the relationship between dopamine D2-like receptors and premature responding, with D2-like receptor antagonism increasing and decreasing impulsivity in the shell and core, respectively.[163]

The evidence for a dopaminergic influence on waiting in the DRL task is limited. However, administration of amphetamine impairs DRL performance, and this effect is blocked by dopamine receptor antagonists.[164]

Norepinephrine and action inhibition

Noradrenergic mechanisms are also implicated in action inhibition. Inhibitors of the norepinephrine transporter have been shown to facilitate action inhibition in the stop-signal task in both rats and humans.[122,165–167] Direct injection of atomoxetine or the alpha-2A adrenoceptor agonist guanfacine into the PFC is able to alter stop-signal inhibition,[168]

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providing evidence that prefrontal norepinephrine regulates response inhibition in this task. Additionally, reversal learning has also been shown to be improved by inhibition of the norepinephrine transporter[169,170] and by stimulation of the alpha-2A adrenoceptor.[171]

Norepinephrine and waiting

Similar to the case with stop-signal and reversal-learning performance, inhibition of the norepinephrine transporter reduces anticipatory responding in the 5CSRTT[165,172] and facilitates waiting in the DRL task.[61] It is as yet unknown why interfering with the norepinephrine transporter produces the most consistent positive effects of the various forms of inhibitory-response control.[173]

Summary

In the preceding section, we reviewed some of the evidence relating measures of action inhibition and waiting (collectively thought to measure aspects of inhibitory response control) to impulsivity and substance-abuse behaviors. We also discussed the underlying neural circuitry and neuropharmacology of these measures. What is clear is that action inhibition and tests of waiting do not relate to two distinct patterns of underlying neural circuitry (Fig. 1), nor do they exhibit two internally consistent but differentiable patterns of pharmacological response (Table 2). Instead, measures of both action inhibition and waiting can depend upon similar brain regions and neurotransmitter systems, while individually exhibiting idiosyncratic responses to manipulations of particular receptor subtypes. From a big picture perspective, this means that the conceptually attractive organization of phenotypes related to inhibitory response control does not present stronger within-category consistency than between-category differences in relation to their underlying biological substrates. Perhaps by comparing this collection of tasks to other even more conceptually distinctive measures of impulsivity (e.g., impulsive choice), further support for the validity of these categories will be revealed; this is the subject of the next two sections of this article.

Delay-related decision making

Reward-seeking behavior is under the control of brain systems that set a value for the outcome being sought. It is almost universally true that the value of rewards decrease (are discounted) as a function of the delay to their delivery, but the rate at which this value is discounted as a function of delay varies across individuals and species.[174] Organisms with rapid discounting rates tend to select actions and responses that lead to immediate outcomes and may therefore engage in a type of impulsive behavior marked by an abnormal preference for immediate gratification, even when it comes at the expense of overall reward receipt. This section deals with the phenomena of delay discounting, which has been conceived of as an independent form of impulsive decision making, as well as its underlying neurobiology.

Conventional tests of delay-related decision making

Delay-related decision making is measured by various delay-discounting procedures (Table 1), each of which generally involving choices between an immediately delivered small reward and a delayed larger reward; either the magnitude or delay can be varied orthogonally to yield equivalent frequencies of selection of the two options (i.e., the indifference point).[175] Choice behavior can be plotted against delays, yielding a hyperbolic curve that estimates the devaluation of reward value by virtue of the delay to its receipt.[176] In human studies, these can include hypothetical or actual monetary rewards, as well as hypothetical negative health outcomes and drug rewards.[175,177] Studies in nonhuman subjects often employ procedures in which operant responses are used to obtain a reinforcer (e.g., food, water, or drug), ranging from maze-based tests to variations of choice procedures involving delay to reinforcement.[30,178,179] In both contexts, despite differences in the type and magnitude of reinforcement and/or delay, the discount functions obtained across species are similar (i.e., hyperbolic in shape); however, the discounting rate, or the steepness of the curve, varies.[180]

Relationship to impulsive temperament

Laboratory measures of the discounting of delayed rewards have been shown to be positively correlated with self-reported measures of impulsivity, as indexed by the Barratt impulsiveness scale, in some studies, but not in others; this discrepancy could be due to analyzing total scores versus scores on each subscale of the questionnaire.[181] In that sense, sensitivity of choice behavior to delay is not necessarily

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clearly associated with personality measures of impulsivity.

Relationship to substance-use disorders

Heightened propensity to discount delayed rewards has been reported in humans with a long-term history of consumption of various drugs of abuse.[182] In humans, the discount of delayed rewards is positively correlated with family history of drug-use disorders, suggesting that it may be a potential risk factor.[183] Similarly, steep delay discounting is associated with self-reported early onset of alcohol use[184] and smoking initiation in adolescents.[185]

Similarly, preclinical studies in rats show that greater delay discounting can predict elevated alcohol, cocaine, and methamphetamine self-administration rates, escalation of cocaine intake, increased nicotine-seeking during abstinence, and greater vulnerability to cue-induced nicotine reinstatement.[84,186–190] A propensity for steep delay discounting may also be a consequence of drug use, as exposure to stimulant drugs increases delay discounting in rodents,[191,192] and drug-paired contextual stimuli can also elicit a state of impulsive decision-making behavior, as rats exhibit an increase in delay discounting in a cocaine-paired context.[193] In this sense, delay-related decision-making phenotypes relate to drug-taking behaviors in humans and animals in a manner not unlike the tests of impulsive action inhibition.

Neural circuitry of delay-related decision making

The neural circuitry involved in delay-related decision making is shown in Figure 1, in comparison with the brain regions implicated in inhibitory response control. Activity in both the ventromedial and dorsolateral PFC, as well as the posterior cingulate cortex, is associated with the discounted value of future rewards in human subjects.[194–196] Moreover, heightened discounting is observed in patients with ventromedial PFC or medial orbitofrontal cortex damage.[197] However, in rats, medial PFC lesions do not alter discounting,[198] while lesions of the orbitofrontal cortex yield equivocal results—increasing delay discounting in one study and decreasing it in another;[199,200] in humans, greater lateral orbitofrontal cortex activity is associated with less discounting.[201]

Activity in the anterior cingulate cortex and the lateral PFC is associated with response times during delay discounting, potentially reflecting the degree of cognitive control over impulsive choices.[202,203] Indeed, disruption of lateral PFC function via repetitive transcranial magnetic stimulation increases choice for immediate rewards over larger delayed rewards.[204]

Additionally, the nucleus accumbens core, hippocampus, and basolateral amygdala have also been implicated in choice tasks, as damage to these areas impairs performance in delay discounting.[198,200,205] While their specific contributions are less well understood, these regions are thought to represent potential future outcomes of decisions.[206]

Peters and Buchel[206] have proposed that these areas can be viewed as distinct neural networks, based on the aspect of decision making they are involved in: a valuation network being the subjective worth of discounted rewards, comprising the ventromedial PFC, medial orbitofrontal cortex, ventral striatum, and posterior cingulate cortex; a cognitive control network reflecting decision conflict and degree of exertion of cognitive control, comprising the anterior cingulate cortex and lateral PFC; and a prospection network reflecting prediction, affect, and prospection processes in decision making and comprising the medial temporal lobe (namely hippocampus and amygdala), with the ventromedial PFC and posterior cingulate cortex being involved in both valuation and prospection networks.

Pharmacological regulation of delay-related decision making

The sensitivity of delay-related decision making to various pharmacological manipulations of monoamine transmission are shown and compared with the effects on impulsive action in Table 2. Serotonin neurotransmission has often been implicated in delay-related decision making. In general, depletion of serotonin results in an increased preference for the small immediate reward, while pharmacologically induced serotonin release increases preference for the large delayed reward.[207–209] However, other studies have also shown serotonin antagonism to decrease delay discounting and forebrain serotonin depletion to have no effect on performance.[116,178] No studies have explored the role for 2A and 2C subtypes of serotonin receptors in delay-related decision making.

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Pharmacologically induced decreases in dopamine activity also yield mixed results in delay-discounting behavior. Antagonism of both D1 and D2 receptors increases discounting of delayed rewards in some studies, while having no effect in others.[210–212] Similarly, increasing dopamine levels via L-DOPA administration has been shown to increase delay discounting; however, amphetamine and dopamine reuptake inhibitors can either decrease or have no effect on delay discounting in rodents and humans, respectively.[212–215] Inconsistent relationships between dopamine and delay discounting may be due to individual differences in baseline dopaminergic signaling,[216] as differences in baseline availability of dopamine autoreceptors in the substantia nigra/ventral tegmental area predict increased discounting.[217]

Consistent with its effects on multiple forms of action inhibition, the noradrenaline reuptake inhibitor atomoxetine reduces choice for small immediate rewards in rats.[165]

Summary

The proclivity to choose actions that lead to immediate gratification, at the expense of other—arguably more rational and optimal—behaviors is thought to reflect a distinct aspect of impulsivity from phenotypes linked with impulsive action. The preceding section dealt with the relationship between delay discounting and substance-abuse behaviors, as well as the underlying neural circuitry and neuropharmacological mechanisms that mediate this form of impulsive choice. While differences in mechanism between inhibitory response control and delay discounting have been reported, it is also clear that the two dimensions of impulsivity share, at least in part, biological influences. The next section will add to this comparison by considering yet another conceptually distinctive dimension of impulsivity related to risk assessment, preference, and aversion.

Risk-related decision making

The risks associated with choices also affect decision making. Many decisions that involve procuring a potential reward also engender risks of reward loss or even explicitly negative consequences (punishment). It is of substantial interest why some individuals are prone to make poor-quality decisions, sometimes repeatedly and after having directly experienced the negative consequences of their behavior, as in the case of individuals diagnosed with drug or alcohol dependence;[48] indeed, risky decision making may be a core phenotype associated with substance dependence, and therefore may also be a target for intervention.

Conventional tests of risk-related decision making

A variable set of tasks has been used to capture behavioral sensitivity to risk (some of which are described in Table 1). These tests all feature choices for high-value reward seeking in the face of risk of forfeiture or punishment, as compared to choice for low-value reward seeking that is more certain or safer.

The Iowa gambling task[218] is a game wherein subjects may sequentially choose from any of four decks of cards. Each card is associated with a gain or loss in points/money. Commonly, two decks yield larger rewards but are also subject to a high rate of large penalties, while the other two yield small rewards but fewer penalties. The payout schedules are arranged such that across the testing session, it is ultimately disadvantageous to select the high reward/penalty decks. The common dependent variable is the difference between the numbers of advantageous versus disadvantageous choices. Generally, control (unaffected) subjects start out by selecting the disadvantageous deck but update their behavior appropriately as the task progresses and they accumulate experience with the outcomes.

The rat gambling task[219] was designed to mimic the structure of the Iowa gambling task. In the rat version, animals are given a limited amount of time to select from four options. As with the decks in the Iowa gambling task, there are two choices with larger potential rewards (more sugar pellets) but also the chance of a large penalty (a long time-out period). The other two choices deliver smaller rewards, but also have shorter time-out penalties. Since time to perform the task is limited, optimal performance involves selection of the smaller reward with shorter time penalty options.

The risky decision-making task[220,221] is a rodent task that operates similarly to the gambling task described above but that implements stronger aversive punishment. Here, rats must choose between either a small-reward safe lever or a large-reward risky lever, which sometimes results in an electric foot shock.

The probabilistic discounting task[222] also requires rats to choose between two levers. The

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small/certain lever guarantees the delivery of one food reward pellet, while the large/risky lever may deliver four pellets with a given probability. Typically, the probability of reward delivery for the large/risky lever descends across four trial blocks from certain (100%) to unlikely (12.5%), producing a shift in optimal choice across the session and allowing for a parametric assessment of risky decision making.

The betting task[223] is designed to assess sensitivity to betting magnitudes when outcomes are actually probabilistically equivalent, a form of irrational choice bias in the face of risk. Here, rats may again choose between safe and risky levers. The latter delivers either twice the value of the safe lever or no reward at 50:50 odds; thus, both levers have equal utility, but the size of the bet can be varied to identify wager-sensitive and -insensitive rats.

The balloon analog risk task (BART) is a computerized task[224] that measures sequential economic risk-taking behavior. In this task, the subject is presented with a picture of a balloon on a computer screen and is given the option to press two buttons. One button inflates (or pumps) the balloon, and each inflation results in the accrual of a small amount of reward (monetary or a points system). Subjects may choose to press the other "cash out" button at any time to add the earned rewards to their guaranteed "bank." With every pump, however, there is a chance that the balloon will burst on the screen, and reward for that trial is forfeited. In the task, optimal performance consists of pumping the balloon enough to maximize reward, while avoiding over-accumulating risk. The main dependent variable studied is the mean number of pumps produced on nonburst trials.

The rat balloon analogue risk task[225] operates similarly to the human version and is adapted for use in operant boxes. Here, rats press on one lever to accumulate food rewards that can be cashed out and received at any time by pressing on a second lever. However, a certain risk is applied such that an additional accumulation press may result in forfeiture of accumulated reward for that trial and a time-out.

The Cambridge gambling task[226,227] is a computerized task wherein subjects are asked to place bets on the location of a hidden token. Unlike in other tasks, the odds of guessing correctly are presented to the subject explicitly by varying the ratio of colors among boxes that may contain the token, and subjects are free to choose the size of their wager. Common outcomes measured include the speed of decision making, frequency of making fewer probable choices, risk tolerance (the mean wager), and risk adjustment (the degree to which subjects vary their wager size on the basis of the parametrically varied explicit odds).

Relationship to substance-use disorders

If the general hypothesis that drug users are more risk prone is true, quantified levels of risk-taking propensity theoretically should discriminate between drug-dependent individuals and controls. Some tasks report this discrimination while others do not in certain populations, possibly due to the nature of optimal performance in the tasks, as will be detailed below.

The Iowa gambling task and Cambridge gambling task have been used to identify differences in decision making between individuals with substance-use problems and controls. In the Iowa gambling task, heavy users of cannabis, stimulants, and alcohol tend to suboptimally perform as compared to matched controls by failing to update their choice behavior and instead continuing to select disadvantageous decks across the test session.[228–230] This pattern of behavior may be linked with insensitivity to the future consequences of disadvantageous choices[231,232] or insensitivity to negative reinforcement.[233] Similarly, in the Cambridge gambling task, stimulant, alcohol, marijuana, and opiate abusers select suboptimal risky bets and had increased deliberation times in some circumstances compared to healthy controls.[227,234,235]

Data from the balloon analogue risk task, however, are mixed with reference to their value as predictive of drug-use problems. Among young adults and adolescents, greater risk taking in the BART is associated with increased use of alcohol and other drugs.[224,236,237] Alternatively, other studies have found that young adult tobacco users take less risk in the BART than nonsmoking controls,[238] and that among a large sample of adults with alcohol-use problems, greater risk taking in the BART predicted less severe clinical symptomatology.[239,240] Dean *et al.*[238] have suggested that this negative relationship may be due to the risk taking being confounded with delay discounting since task performance

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requires persistence and patience; furthermore, unlike the other tasks described here, reduced risk taking in the BART is, in the economic sense, a suboptimal strategy since diminished risk taking ultimately results in smaller earnings.

Data from rodent models examining the effects of acute drug-of-abuse exposure on risky decision making have yielded mixed results. Morphine and ethanol did not have significant effects on behavior in the risky decision-making task.[220] Acute nicotine administration[241] and amphetamine[222] increased selection of the large/risky lever in the probabilistic discounting task where the risk is for a time-out. On the other hand, a lower dose of nicotine and higher dose range of amphetamine decreased selection of the risky lever in the risky decision-making task, where subjects risk a foot shock.[220,242] While nonlinear effects of drugs on behavior are not atypical, it appears here that the nature of punishment (reward forfeiture versus active shock) may also modulate the effect of these drugs on choice behavior.

Neural circuitry of risk-related decision making

Interpretation of neuroimaging data obtained from patients and controls during tests of risk-related decision making is a significant challenge, as broad neural networks are involved and the designs of some tasks limit their implementation in event-related fMRI analysis. However, animal models offer an opportunity for controlled investigation of relevant circuitry. For a more detailed review of the neural circuitry implicated in specific components of risk-related decision making in addiction, see Diekof, Falkai, and Gruber.[243] Below, we outline recent human and rodent data that implicate a frontal–striatal network in regulation of behavior in these tasks; these results are presented graphically in Figure 1.

The Iowa gambling task was initially implemented in patients with ventromedial PFC damage;[218] these individuals exhibit remarkably poor performance in the task, despite being unaffected in many other intellectual dimensions. Pharmacologic inactivation studies in rats demonstrated the roles of the basolateral amygdala and the orbitofrontal cortex in performance of the rat gambling task.[244] Functional disconnection studies have also shown the importance of communication between the basolateral amygdala and either the nucleus accumbens or the PFC in choice behavior in the probabilistic discounting task.[245]

Similar regions are identified even when probabilities of outcomes are known, as in the Cambridge gambling task. Here, patients with ventromedial PFC damage consistently bet more than healthy controls, and those with insula damage failed to appropriately decrease their bets as the odds of winning decreased.[246] Furthermore, in healthy adolescents, increased risk taking in the Cambridge gambling task is associated with diminished ventral striatal response to reward anticipation.[235]

Neuroimaging of control and substance-using subjects performing the BART has implicated a partially overlapping network of brain regions. Brain regions implicated in risk acceptance include the anterior insula, the anterior cingulate, the dorsolateral PFC, and deactivations of the ventromedial PFC. [247–249] Activity in the amygdala was found to promote risk aversion after loss in the BART.[249,250] Pharmacologic inactivation studies in rats have confirmed a role for the ventromedial PFC and the orbitofrontal cortex in aspects of risk taking in the rat BART.[225] Furthermore, striatal D2/D3 dopamine receptor density was negatively correlated with the degree to which dorsolateral PFC activation was modulated by risk taking,[250] highlighting the interaction between these systems in updating potential reward values and guiding goal-directed behavior.

Pharmacological regulation of risk-related decision making

Data on the neuropharmacological basis of risk-related decision making are emerging; some of the results discussed below are also presented in Table 2 for comparison purposes. The hypothesized role of serotonin in the decision-making process involves its regulation of the affective and behavioral responses to negative feedback.[251] Serotonergic depletion produces a pattern of impaired decision making in the Cambridge gambling task similar to that observed in substance-use disorders.[227] On the other hand, a serotonin-1A agonist (8-OH-DPAT) impaired performance in the rat gambling task[219] while a selective serotonin reuptake inhibitor (citalopram) had no effect,[252] suggesting that the relationship between serotonin and optimal decision making is not necessarily linear.

Dopamine, however, may influence nonaffective aspects of decision making related to learning and

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evaluating risk and reward levels. Although the effects are not uniform, pharmacologic stimulation and suppression of the dopamine system using systemic D1 and D2 receptor agonists and antagonists can bias choice behavior in some rodent tasks.[219,221,222,252] These effects may involve activity at D1 dopamine receptors (but not D2) in the nucleus accumbens.[253] Microdialysis measurement of dopamine efflux during the probabilistic discounting task in the PFC and nucleus accumbens, respectively, suggests that the former encodes relative reward rate or availability while the latter encodes an integration of reward rate, uncertainty and preference, and decision information.[254] Additionally, striatal D2/D3 density as assessed by micro-PET in rats was negatively correlated with wager sensitivity in the betting task,[223] implicating this system in irrational choice bias in the face of uncertainty. In sum, aggregate data indicate that dopamine signaling in brain regions implicated in decision making and learning processes influence behavior in these risky decision-making tasks, but the precise mapping of signals at specific receptor subtypes in these networks onto specific decision making–related functions remains to be resolved.

Finally, there have been few studies investigating the influence of the norepinephrine system. In particular, the norepinephrine reuptake inhibitor atomoxetine alone did not alter decision making in the rat gambling task, but it did increase choice of the disadvantageous lever when combined with a specific dopamine reuptake inhibitor.[252]

Summary

Risk-related decision making appears to predict susceptibility for substance use disorders in humans and addiction-related behaviors in animals, but the progression of drug experience appears to alter these relationships, producing task-specific changes in impulsive decision making. While less is known about the underlying mechanistic basis of risky decision making, from the neural circuitry and pharmacological perspectives, it is evident that this domain at least partially shares a neural circuitry and neuropharmacology with inhibitory response control and delay discounting (Fig. 1; Table 2). A great deal more work needs to be conducted to compare tests of risky decision making to one another and to the other dimensions of impulsivity discussed above.

Impulsivity in addiction: multidimensional?

In the preceding sections, we presented some of the data linking certain manifestations of impulsive behavior (Table 1) to drug seeking and taking, and we provided a survey of the involvement of frontostriatal (Fig. 1) and monoaminergic mechanisms (Table 2) to these relationships. Perhaps the strongest conclusion to be drawn from this work is that the relationship between impulsivity and addiction-related behaviors is very strong. In human subjects, there appears to be a robust association between self-report measures of impulsivity, laboratory tests of impulsive behavior, and recreational and clinically impairing patterns of drug and alcohol abuse and dependence. Deficits in action inhibition, waiting, delay discounting, and risk-related decision making are all found in various populations affected by substance-use disorders, and burgeoning evidence suggests that some of these deficits (including impairments in action inhibition, delay discounting, and risky decision making) predate the onset of pathological drug taking (and possibly anticipate all drug use). Research using animal models expands on this data by providing definitive evidence that individual differences in the propensity to engage in impulsive behavior predicts aspects of drug self-administration behaviors, and experience with the pharmacological effects of drugs, over the long term, can cause abnormalities in action inhibition, waiting, delay discounting, and risk-related decision making. For all these reasons, and despite some inconsistency in the literature, impulsive behaviors do appear to play key roles in the various stages of substance use, abuse, and dependence.

As indicated in the introduction, a dominant hypothesis in the field is that there are various forms of impulsive behavior that may each contribute in unique ways to understanding addictions. This hypothesis emerged mostly because of descriptive differences between the purported subtypes (e.g., inhibiting an inappropriate behavior seems conceptually very different than reasoning about a delayed reward or risky outcome). Stronger evidence for this notion might include (1) independent determination of individual differences in performance of various tests of impulsivity in both humans and animals, (2) unique statistical relationships between

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each measure of impulsivity and addiction (i.e., each phenotype is predictive of or affected by exposure to drugs of abuse in dissociable ways), and (3) different underlying neurobiological mechanisms that configured each form of impulsive behavior.

Relatively few studies have conducted a systematic effort to examine patterns of covariation in forms of impulsive behavior in animals or humans, and even fewer have conducted an adequately designed study. In rats, two separate studies suggest that action inhibition in the 5CSRTT does not predict delay-discounting ability. [255,256] In human subjects, behavioral measures of action inhibition and delay-related decision making did not correlate with one another or with subjective self-report measures.[255] Caution should be taken when interpreting these results, however, since comparing two phenotypes often magnifies the differences and minimizes the similarities. Moreover, this approach cannot separate differences in task from differences in the construct(s) intended to be measured. Instead, an ideal design for studies of this type involves multiple assessments of both related and unrelated phenotypes. Additionally, inbred rodent or human twin designs are required to separate shared genetic influences that span across tasks from other factors.[256]

The extent to which different phenotypes related to impulsivity predict unique proportions of the liability for addiction-related behaviors has not been entirely explored, but the available data indicate that a number of the measures are linked with a heritable susceptibility for drug use in humans and animals. Tests of action inhibition (stop-signal inhibition,[257] 5CSRTT,[83,84] and reversal learning[80]), delay discounting,[32] and risky decision making[258] all appear to have a predictive value in this regard. While few studies have directly compared their predictive value using standardized procedures, one such study that did suggested that action inhibition and delay discounting predicted dissociable aspects of drug self-administration.[84]

The evidence that each of these measures predicts elevated propensity to self-administer drugs is not consistent with the idea that the tests are uniquely predictive, though clearly more systematic work needs to be done to evaluate the notion that putative subtypes of impulsivity are associated with different dimensions of drug self-administration behaviors, and again, more sophisticated designs must be undertaken before it can be determined whether these correlations are genetically mediated, and whether shared genetic factors underscore the relationship between different measures of impulsivity and addictions.

The underlying biological mechanisms (both circuitry and molecular mechanisms) necessary for performance of various tests of impulsivity are not identical, but a core set of frontostriatal circuits is repeatedly implicated in various types of impulsivity and decision making. As shown in Figure 1, there is a distinction between measures of impulsive behavior that rely upon more lateral, orbital regions of the frontal cortex and those that rely on ventromedial, limbic portions. At the neuropharmacological level, there are also important distinctions, with responses to acute challenge with monoaminergic drugs and/or responses to chronic administration of addictive drugs being task specific (Table 2).

At the same time, one cannot ignore their remarkable similarity. For example, it is true that various forms of impulsivity, including 5CSRTT, reversal learning, and delay discounting, all predict enhanced acquisition of stimulant self-administration.[80,83,187–190,259] Moreover, the neural circuitry underlying the tasks contains a great deal of overlap, particularly in the medial orbital regions of the frontal cortex and the dorsomedial regions of the striatum (discussed above and summarized in Fig. 1). Finally, there is consistency of evidence that low dopamine D2 receptor function and alterations in serotonin-2A and -2C receptors are involved in many forms of impulsivity discussed here.[2,31,79,83,139,155,162,163,212,217,260–265]

How can one resolve the facts that these arguably separable forms of impulsivity (1) each have qualitatively similar patterns of predictive value of substance use disorders in humans and drug self-administration in animals, (2) each depend upon partially overlapping neural circuitries, and (3) are each sensitive in similar ways to monoaminergic manipulations? Figure 2 shows two potential models that could explain these facts; these two models are certainly not the only possibilities but may be instructive in guiding future studies. One model (Fig. 2A) suggests that each of the forms of impulsivity share some variance and mechanisms with one another but that each shares a unique set of variance and mechanisms with addictions. This model says that the correspondences in Figure 2 and

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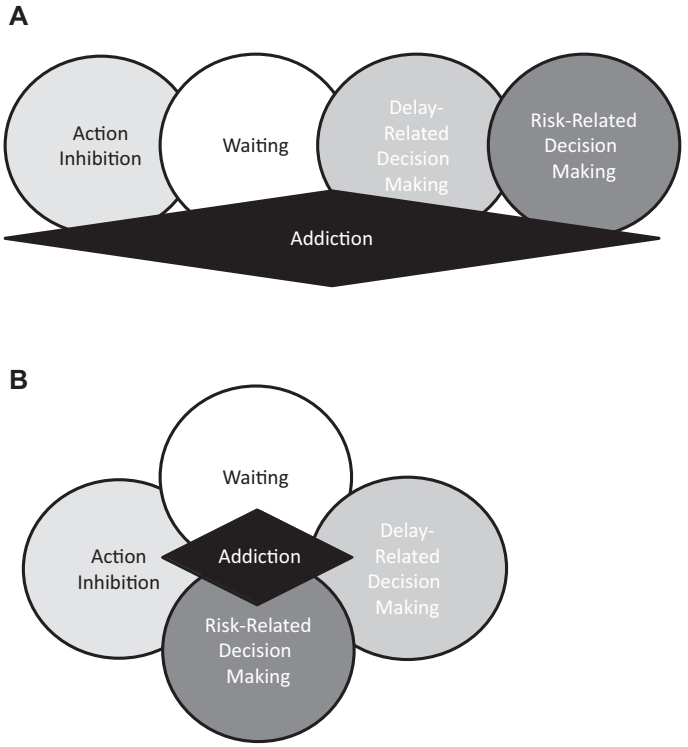

Figure 2. **Hypothetical models possibly explaining the relationships between forms of impulsive behavior and addiction. One model (A) proposes that each manifestation of impulsivity shares unique variance and mechanisms with addiction behaviors. Another (B) suggests that these varieties of impulsivity share a small but measurable amount of variance and numbers of mechanisms between them and that it is this overlap that is shared between them and addictions.**

Table 2 are instructive about the relationships between forms of impulsivity but not about their individual relationships to addictions. It suggests that other mechanisms, perhaps unknown to use, explain these individual predictive relationships.

Another model (Fig. 2B) suggests that the various forms of impulsivity once again share a portion of their variance and mechanism with one another and with addiction-related behaviors. It suggests that these tasks may well only share limited amounts of variance and numbers of mechanisms but that this small similarity is exactly what links them each to addictions. In this case, the brain mechanisms they share in common should also be biomarkers often found in clinical drug addictions. It is notable, in this regard, that relatively low brain dopamine D2 receptor availability is both a biomarker for impulsive tendencies[1,31] and for substance-use disorders.[155,266] Moreover, drug addictions have repeatedly been linked to structural and functional abnormalities in the same circuits implicated in impulsivity, namely the ventrolateral frontal cortex, the ventromedial frontal cortex, and the limbic regions of the striatum.[54,266–271] From this perspective, a core set of neuroadaptations involving (perhaps) orbital and ventromedial frontal cortical dysfunction, reductions in brain dopamine D2 receptor signaling, and/or altered serotonergic transmission that results from genetic or early environmental mechanisms or from experience with the pharmacological effects of drugs of abuse result in a pattern of impulsive action and choice that are due to shared mechanisms. This is an important hypothesis to test, whether it proves to be correct or incorrect.

New directions for research on impulsivity and addictions

One of the most promising areas of work described above is the research that identifies aspects of impulsive behavior as quantitative indicators of liability for the initiation of substance use, of its

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transition to a more compulsive form of substance abuse, and of successful treatment of substance dependence. Because impulsivity predates substance use in many circumstances and because impulsivity is itself a heritable trait,[272] the discovery of genetic influences on impulsive behavior is crucial. Using human subjects, studies of related individuals (particularly monozygotic and dizygotic twins) can be used to model the genetic relationships between putatively distinct forms of impulsive behaviors and substance use, abuse, and dependence. In the preclinical laboratory, isogenic rodent strains (inbred rats and mice)[256,273] or pedigreed nonhuman primates[274,275] can also be used to separate genetic from shared environmental factors. Moreover, advanced lines of mice—including recombinant inbred mice,[276,277] the hybrid mouse diversity panel,[278] and the diversity outcross[279]—are now available for identifying the genetic and genomic factors that may be unique to, or shared between, measures of impulsivity that each predict susceptibility to drug self-administration and addiction-related behaviors. Because of the advent of highly sophisticated genetics resources that can uncover biological influences never before considered, it is crucial that the relationship between dimensions of impulsivity and addictions be dissected at the behavioral and neural circuitry level. By doing so, we may make progress toward understanding the concept of susceptibility for addictions at all levels of analysis, from genes to cells to circuits to behavior.

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Conflicts of interest

The authors declare no conflicts of interest.

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