Current Topics in Behavioral Neurosciences 47

Harriet de Wit
J. David Jentsch *Editors*

Recent Advances in Research on Impulsivity and Impulsive Behaviors

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Preface

The concept of impulsivity, and its role in both normal and pathological behavior, has become a major topic of research over the past 30 years. According to PubMed, the number of publications on impulsivity and inhibitory control has increased from about 700 in 1990 to well over 4000 in 2019. We have made major advances in our understanding of the behavioral processes that comprise what we refer to as "impulsive" behavior, as well as its neural and genetic underpinnings. Impulsive behaviors are involved in almost every psychiatric disorder, most notably in drug use disorders, externalizing behaviors, and childhood disruptive behavior disorders. This volume brings together recent findings from several of these areas, written by experts in the respective fields. We bring together a number of sometimes disparate topics, including empirical studies with laboratory animals, healthy volunteers and patients, and address theoretical analyses as well as practical considerations.

The first section addresses what is known about the neurobiological basis of impulsive behaviors. Pattij and Vanderschuren first introduce the different types of impulsive behavior, and some of the challenges in harmonizing studies with humans and nonhuman species, and then review the evidence for the involvement of dopamine and norepinephrine, as well as some novel targets including opioid receptors and ErbB signaling pathways. Although early studies focused on serotonin as a key neurotransmitter in impulsive behaviors, this review demonstrates that impulsive behaviors are controlled by a broader array of neurotransmitter systems. Groman similarly reviews the procedures typically used to study impulsive behavior, and then examines these procedures from the lens of reinforcement learning, and temporal difference signals. She examines the evidence for the respective roles of several neurotransmitter systems in reinforcement learning and risky decision-making, arguing that these comprise the basic components of impulsive behavior. London examines what is known about the neural processes involved in impulsive decision-making from the point of view of human imaging studies such as PET and fMRI, in both healthy adults and in patients. Specifically, she points to the importance of striatal D2-type dopamine receptors and corticostriatal connectivity in cognitive control, impulsivity, and response inhibition. Such information is critical to develop possible therapeutic targets for disruptive

impulsive behaviors. Weafer reviews the recent evidence of sex differences in brain engagement during inhibitory control. Inhibitory control is one form of impulsive behavior, and there is evidence that there are sex differences in the neural correlates of successful and unsuccessful inhibitions. The author notes that there is a lack of comprehensive data on sex differences and the role of circulating hormones in the neural processes underlying inhibition.

The next section of the book examines more closely some of the behavioral manifestations of impulsive behavior. Barr and Dick focus on the role of impulsive choice and impulsive action in externalizing behaviors, using data from human genetic studies. They summarize the evidence for the heritability of externalizing behaviors, and how these behaviors change over developmental stages and in interactions with the environment. They also summarize recent whole genome studies with phenotypes related to impulsivity, showing that these behaviors have clear genetic underpinnings. Levitt et al focus on one form of impulsive behavior, namely delay discounting. They review the evidence for the importance of delay discounting in addiction, attention deficit/hyperactivity disorder, and obesity, and discuss both environmental and genetic factors that influence these behaviors. Bickel et al provide a unique perspective on delay discounting, with their Reinforcer Pathology Theory. This theory describes the interaction among strong preferences for immediate rewards, insensitivity to negative consequences, and over-valuation of specific commodities that offer brief, intense reinforcement. This theoretical framework provides novel avenues for modulating the valuation of reinforcers (e.g., working memory training, TMS).

The final series of chapters addresses topics of direct clinical relevance. Liu et al discuss developmental trajectories of impulsive behaviors across the lifespan, with a particular focus on middle to older adulthood. Impulsive behaviors are common among adolescents and young adults, but a small but significant subset of adults continues to exhibit these behaviors, with negative consequences including substance abuse. The authors note that these behaviors are often accompanied by emotional states such as negative urgency, pointing to the important link between affect and cognition. Swann et al discuss the role of impulsivity in suicidal behaviors, noting important links between negative affective states or depressive symptoms and impulsive action and impulsive choice. They also review some of the neurochemical mechanisms believed to be involved. Herman and Duka examine the role of impulsive behavior in the context of alcohol use disorders, with careful consideration of the different forms of impulsive behavior that affect drug use. They also review some of the literature on the neural correlates of impulsive behaviors.

Collectively, the chapters that constitute this volume highlight a number of current issues in the study of impulsivity and impulsive behaviors, address some of the relevant challenges and controversies and outline relevant future directions for related research.

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Contents

Part I
Neurobiology: Preclinical and Clinical

The Neuropharmacology of Impulsive Behaviour, an Update

Tommy Pattij and Louk J. M. J. Vanderschuren

Contents

Abstract Neuropharmacological interventions in preclinical translational models of impulsivity have tremendously contributed to a better understanding of the neurochemistry and neural basis of impulsive behaviour. In this regard, much progress has been made over the last years, also due to the introduction of novel techniques in behavioural neuroscience such as optogenetics and chemogenetics. In this chapter, we will provide an update of how the behavioural pharmacology field has progressed and built upon existing data since an earlier review we wrote in 2008. To this aim, we will first give a brief background on preclinical translational models of impulsivity. Next, recent interesting evidence of monoaminergic modulation of impulsivity will be highlighted with a focus on the neurotransmitters dopamine and noradrenaline. Finally, we will close the chapter by discussing some novel directions and drug leads in the neuropharmacological modulation of impulsivity.

Keywords Behavioural neuroscience · Dopamine · Noradrenaline · Pharmacology · Translational models

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A little over a decade ago, we wrote a review on impulsivity on the occasion of the celebration of 100 years of pharmacology research in the Netherlands. This review addressed the neuropharmacology of impulsivity, focusing on the collective work from preclinical translational models of impulsivity (Pattij and Vanderschuren 2008). At that time, the study of the neural basis of impulsivity relied on behavioural pharmacological intervention techniques in preclinical translational animal models. Other often-used intervention techniques back then – and still today – consisted of, for instance, performing selective (neurochemical) lesions/disconnections of brain regions, conducting targeted gene deletions (primarily in murine models) and measuring mRNA/protein/neurotransmitter levels in selected brain regions.

Since then, the introduction of novel genetic techniques such as optogenetics and chemogenetics has created unique opportunities to manipulate brain function in a cell-type-specific, circuit-specific and bidirectional manner (see for recent reviews on these techniques: Rajasethupathy et al. 2016; Roth 2016). These novel techniques have revolutionized behavioural neuroscience, which is also contributing to our understanding of the neurobiology of impulsivity (see for recent review: Carr et al. 2018). However, whereas optogenetic and chemogenetic approaches have provided detailed fundamental knowledge of the neural underpinnings of cognition – in a projection and/or cell-type-specific way – from a clinical perspective, there are many hurdles to be overcome before these novel techniques can be implemented for therapeutic purposes on a large scale. As such, behavioural pharmacological systems approaches are closer to clinical implementation and still provide valuable insights into the neurochemical basis of impulsivity, despite some of the obvious disadvantages such as off-target tissue or off-target receptor effects of drugs (Berger and Iyengar 2011) and blood-brain barrier limitations (Patel and Patel 2017). In this chapter, we will give an update of how the behavioural pharmacology field has progressed and built upon existing data since our 2008 review. We will focus on two neuromodulator systems widely implicated in impulsivity – i.e. dopamine and noradrenaline – as well as novel targets that have emerged from the field.

1 Preclinical Translational Models of Impulsivity

Most of our understanding of the neural basis and neurochemistry of impulsivity is derived from rodent experiments. The majority of this work has been carried out using rats as model species, yet since the availability of genetically engineered mouse models (Capecchi 2005), mice also have been used to study the neurobiology of impulsivity.

To this aim, various operant tasks have been developed over the last 40 or so years. Some of these tasks have been directly adopted from human neuropsychological tasks measuring aspects of impulsivity, such as the 5-choice serial reaction time task (5-CSRTT; Carli et al. 1983), the stop-signal task (Feola et al. 2000), Go/No-Go tasks (Terman and Terman 1973) and various temporal and delay discounting tasks (Evenden and Ryan 1996; Mazur 1987; Richards et al. 1997). Other tasks used were originally developed for other purposes, such as differential-

reinforcement-of-low-rate (DRL) schedules of reinforcement, which detect effects of antidepressant drugs (McGuire and Seiden 1980) and at the same time capture aspects of impulsive behaviour. There are many excellent reviews that describe these rodent translational models of impulsivity in detail (see e.g. Eagle and Baunez 2010; Robbins 2002; Winstanley 2011; Yates 2018); we will briefly describe the main principles of the most often-used impulsivity tasks here.

Given the multidimensional nature of the impulsivity construct (Evenden 1999; Dalley and Robbins 2017), these translational models should be distinguished based on the aspects of impulsivity they measure. Typically, a distinction is made between impulsive action and impulsive choice (although one can also distinguish models of 'stopping' and 'waiting'). On the one hand therefore, models are used that measure impulsivity related to the ability to inhibit prematurely expressed behavioural responses or the ability to cancel and disengage from ongoing behaviour. Examples of models measuring these aspects of impulsivity in rodents are the 5-CSRTT, DRL schedules of reinforcement, Go/No-Go tasks and the stop-signal task. Typically, increased impulsivity in such models is exemplified by either high levels of prematurely expressed responses or the inability to inhibit ongoing behaviour. In this chapter, we will refer to impulsive action as an umbrella term when addressing data from these models. On the other hand, delay discounting tasks in which animals have control over delays, c.q. adjusting-delay/adjusting-amount procedures, or do not have control over delays, measure the preference for delayed larger reinforcement over immediate small reinforcement. Such tasks typically generate delay discounting curves, whereby steeper discounting, i.e. a larger preference for immediate small reinforcement, reflects more impulsive choice.

In terms of validity of aforementioned translational models for the impulsivity construct in humans, it would go beyond the scope of this chapter to give a full account of the different validity criteria. Several reviews have eloquently and elaborately discussed the validity and utility of these models (Dalley and Robbins 2017; Eagle and Baunez 2010; Winstanley 2011). Nonetheless, there are some common characteristics of rodent models that differ from human impulsivity tasks that are noteworthy for the reader who is not fully familiar with the rodent literature. For example, the vast majority of rodent impulsivity models use positive reinforcement to train task contingencies and maintain task performance (although some studies require decisions between rewards and punishments; see Simon et al. 2009 and Verharen et al. 2019), for instance, by using highly palatable food pellets or small amounts of condensed milk. This differs from studies in humans, in which the typical reward is often (hypothetical) money, and involves both gains and losses. Monetary losses are difficult to implement in an animal experiment. Also, animals are usually mildly food-deprived to enhance motivation and task engagement; this can impact the interpretation of pharmacological effects. A second important difference between laboratory tests of impulsivity in rodents vs humans is the length of training. In humans, subjects are typically given brief instructions, and a few practice trials before testing. In rodents, prolonged periods of daily training are required before animals achieve stable responding in the tasks. As a result, different memory systems (short-term/explicit in humans, long-term/implicit in animals) may be engaged, which should be taken into account when interpreting data on a systems

neuroscience level. In addition, impulsivity experiments in animals are usually long-lasting and labour-intensive; it is not uncommon that a single experiment can take up to 6 months or longer before completion. To circumvent this, a novel direction is the development of automated home-cage-based approaches of measuring cognition and impulsivity, which (1) allows animals to voluntarily engage in the tasks; (2) tremendously speeds up training time; and (3) reduces possible experimenter-induced interference. Although only a few studies have been published using such an approach to measure impulsivity (Bruinsma et al. 2019; Carr et al. 2018; Koot et al. 2009; Remmelink et al. 2017; Rivalan et al. 2017), the approach is starting to gain interest from the field. This, also since new computational approaches such as, for instance, machine-learning algorithms to analyse video-tracks of behaviour are rapidly developing (Kabra et al. 2013; Kwok 2019; Lorbach et al. 2018) and would allow for integrative analyses of home-cage behaviour with cognitive performance following, for instance, pharmacological manipulations.

2 Monoaminergic Modulation of Impulsivity

Traditionally, most behavioural pharmacological interventions in animal models of impulsivity have focused on the monoamine neurotransmitters dopamine, noradrenaline and serotonin. This fits well with the mechanisms of action of ADHD pharmacotherapies such as amphetamine, atomoxetine and methylphenidate, which generally increase efflux of dopamine, noradrenaline and to a lesser extent serotonin and histamine (for review, see Heal et al. 2009). Since our 2008 review, many studies have further elaborated on the role of dopamine, noradrenaline and serotonin in impulsivity (for recent reviews see Bacqué-Cazenave et al. 2020; Dalley and Robbins 2017; Winstanley 2011). In this chapter we will highlight recent interesting observations, with a focus on dopamine and noradrenaline, since over the last decade, most behavioural pharmacological work has investigated these neurotransmitters (see for overview, Table 1).

2.1 Dopamine

Recent studies have further pinpointed involvement of dopamine D2-like receptors in impulsive action in the 5-CSRTT, building on earlier work showing the importance of dopamine D2/D3 receptors in the ventral striatum in impulsivity (Dalley et al. 2007; Pattij et al. 2007). As such, it was shown that increased impulsive action due to medial prefrontal cortex damage can be reduced by treatment with the selective dopamine D2/D3 receptor antagonist sulpiride into the ventral striatum (Pezze et al. 2009). Subregional ventral striatal dopamine involvement in impulsivity has been demonstrated in several other studies. For instance, the preferential dopamine D3 receptor antagonist nafadotride was found to increase impulsive action in

Table 1 Pharmacological modulation of dopamine and noradrenaline receptor subtypes in impulsivity

Receptor	Agonist	Antagonist	Region	Impulsive action	Impulsive choice	References
Dopamine						
D2		Sulpiride	NA	↓		Pezze et al. (2009)
D2/D3	Quinpirole		NAC	↑		Moreno et al. (2013)
			NAS	=		
D3		Nafadotride	NAC	↓		Besson et al. (2010)
			NAS	↑		
Noradrenaline						
Transporter		Atomoxetine		=		Baarendse and Vanderschuren (2012) and Sun et al. (2012)
				↓		Bari et al. (2009), Benn and Robinson (2017), Blondeau and Dellu-Hagedorn (2007), Broos et al. (2012), Liu et al. (2015), Navarra et al. (2008), Paine et al. (2007), Paterson et al. (2011), Robinson et al. (2008), Sasamori et al. (2019), Sun et al. (2012) and Tsutsui-Kimura et al. (2009)
		Atomoxetine			↓	Bizot et al. (2011) and Robinson et al. (2008)
		Atomoxetine			↑	Broos et al. (2012)
		Desipramine		↓		Pattij et al. (2012)
					↓	Bizot et al. (2011)
		Nortriptyline		↓		Roychowdhury et al. (2012)
Alpha-1		Prazosin		=		Mahoney et al. (2016) and Roychowdhury et al. (2012)
			OFC	=		Adams et al. (2017)
	Phenylephrine			(↓)		Pattij et al. (2012)
					=	Van Gaalen et al. (2006b)
			OFC/ mPFC		=	Pardey et al. (2013)
Alpha-2	Clonidine			(↓)		Pattij et al. (2012)

(continued)

Table 1 (continued)

Receptor	Agonist	Antagonist	Region	Impulsive action	Impulsive choice	References
	Guanfacine			(↓)		Terry et al. (2014)
				=		Mahoney et al. (2016)
			OFC/ mPFC		=	Pardey et al. (2013)
		Yohimbine		↑		Adams et al. (2017), Broos et al. (2017), Funk et al. (2019), Mahoney et al. (2016), Sun et al. (2010) and Schippers et al. (2016)
					↓	Schippers et al. (2016)
			OFC	↓		Adams et al. (2017)
Beta-1/ beta-2	Isoprenaline			(↓)		Pattij et al. (2012)
		Propranolol		=		Mahoney et al. (2016), Milstein et al. (2010) and Roychowdhury et al. (2012)
			OFC	=		Adams et al. (2017)
Beta-1	Dobutamine			(↓)		Pattij et al. (2012)
Beta-2	Clenbuterol			↓		Pattij et al. (2012)

Upward arrows indicate that ligands increase impulsive action or impulsive choice Downward arrows indicate beneficial effects of ligands on impulsivity, and equals signs indicate no behavioural effects of these ligands on impulsivity. Parentheses indicate that the effects were likely secondary to other (motor) effects *mPFC* medial prefrontal cortex, *NA* nucleus accumbens, *NAC* nucleus accumbens core region, *NAS* nucleus accumbens shell region, *OFC* orbitofrontal cortex

the 5-CSRTT when infused into the nucleus accumbens shell region and to decrease impulsive action when infused into the nucleus accumbens core region (Besson et al. 2010). In addition, microinfusion of the dopamine D2/D3 receptor agonist quinpirole into the nucleus accumbens core, but not shell, was also found to increase impulsive action as well as locomotor activity (Moreno et al. 2013). The fact that in this latter study, nafadotride treatment blocked the effects of quinpirole on locomotor activity, but not impulsive action, suggests a dopamine D2 receptor-mediated mechanism in impulsive action. Intriguingly, these pharmacological modulations of impulsivity were only found in animals with high baseline levels of impulsive action, indicating altered dopamine functioning in trait impulsive individuals. This latter notion is supported by abundant neurochemical and pharmacological data in trait impulsive rats. As briefly highlighted above, microPET (positron emission tomography) approaches in highly impulsive rats in the 5-CSRTT have demonstrated reduced binding of the dopamine D2/D3 receptor antagonist ^{18}F-fallypride in the ventral striatum (Dalley et al. 2007), a finding which was later found to be more pronounced in the left hemisphere (Caprioli et al. 2013). Autoradiographic work has further strengthened these PET findings, demonstrating reduced dopamine D2/D3 receptor and dopamine transporter binding in the nucleus accumbens shell, as well as reduced dopamine D1 receptor binding in the nucleus accumbens core in trait impulsive rats as assessed in the 5-CSRTT (Jupp et al. 2013). Other approaches, such as ex vivo neurochemistry, showed differential dopamine release from the nucleus accumbens core and shell region in rats characterized for high impulsive action. Whereas in high trait impulsive rats (tested in the 5-CSRTT) electrically stimulated dopamine release was found to be increased in the nucleus accumbens shell region, dopamine release from the nucleus accumbens core region was found to be decreased (Diergaarde et al. 2008). In addition, high trait impulsive action in a DRL task was associated with increased dopamine D1 receptor gene expression in the nucleus accumbens shell and decreased dopamine D2 receptor gene expression in the nucleus accumbens core (Simon et al. 2013).

Regarding impulsive choice, we found that electrically stimulated dopamine release from both the nucleus accumbens core and shell region as well as the medial prefrontal cortex was decreased in high impulsive rats in a delay discounting task (Diergaarde et al. 2008). Moreover, we and others found that high impulsive choice also correlated with increased dopamine D1 receptor and dopamine D5 receptor gene expression (Loos et al. 2010) and lower dopamine D2 gene expression (Simon et al. 2013) in the medial prefrontal cortex. Recent PET approaches in rats using ^{18}F-fallypride also hinted towards functional changes in dopamine function in trait impulsive choice rats (Barlow et al. 2018), albeit that these changes were less pronounced compared to the findings in trait impulsive action rats (Caprioli et al. 2013; Dalley et al. 2007). Collectively, these data suggest differential involvement of dopamine in corticostriatal circuits in impulsive action and impulsive choice, substantiating earlier pharmacological work (see e.g. Cole and Robbins 1987; Winstanley et al. 2005; Van Gaalen et al. 2006a, b).

Importantly, whereas the preclinical literature on dopamine modulation of impulsivity is extensive, the cumulative work from this field strongly converges with

clinical observations. In this regard, recent human PET studies have reported that trait impulsivity is associated with enhanced amphetamine-evoked dopamine release in the striatum and lower dopamine D2/D3 receptor availability in the midbrain (Buckholtz et al. 2010), as well as altered availability of dopamine transporters in the striatum (Smith et al. 2019).

Taken together, accumulating evidence from both preclinical and clinical work strongly implicates dopamine D2-like receptors in the nucleus accumbens in impulsivity. The distinction between ventral striatal subregions (i.e. nucleus accumbens core and shell), subtypes of dopamine D2-like receptors (most prominently, the dopamine D2 and D3 receptors, whereas the involvement of the dopamine D4 receptor in impulsivity awaits thorough investigation) and impulsive choice vs impulsive action is expected to provide a fine-grained picture of how dopaminergic neurotransmission modulates impulse control. In this regard, involvement of dopamine D1-like receptor signaling and structures beside the ventral striatum (e.g. dorsal striatum and prefrontal cortical regions) in impulsive behaviour should not be overlooked.

2.2 Noradrenaline

Since our 2008 review, many new studies have been published investigating noradrenergic modulation of impulsivity. At the time of our review, the noradrenaline reuptake inhibitor atomoxetine had just entered the market as a newly approved drug for the treatment of ADHD symptoms. Importantly, since then the field has progressed, and many studies have demonstrated beneficial effects of various noradrenaline reuptake inhibitors, including atomoxetine, desipramine and milnacipran on impulsive action and/or impulsive choice in preclinical translational impulsivity models (see e.g. Bari et al. 2009; Bizot et al. 2011; Benn and Robinson 2017; Blondeau and Dellu-Hagedorn 2007; Broos et al. 2012; Liu et al. 2015; Navarra et al. 2008; Paine et al. 2007; Paterson et al. 2011; Pattij et al. 2012; Robinson et al. 2008; Roychowdhury et al. 2012; Sasamori et al. 2019; Sun et al. 2012; Tsutsui-Kimura et al. 2009). Nonetheless, not always beneficial effects of noradrenaline reuptake inhibitors have been reported on impulsivity, or alternatively, such effects were associated with simultaneous task slowing effects (Baarendse and Vanderschuren 2012; Benn and Robinson 2017; Paine et al. 2007; Sun et al. 2012). Altogether, the work with noradrenaline reuptake inhibitors suggests an important role for noradrenaline signaling in impulsivity and indicates that high noradrenaline activity is associated with lower impulsive action and/or impulsive choice. In terms of region-specific involvement of noradrenaline signaling in impulsivity, microinfusions of atomoxetine into the ventral striatum, in particular in the nucleus accumbens core, but not prefrontal cortex were found to mimic the effects of systemic atomoxetine (Economidou et al. 2012). This suggests a stronger involvement of subcortical over cortical noradrenaline in impulsivity. A subsequent elegant study (Benn and Robinson 2017) provided further evidence for this, using a saporin-

conjugated dopamine beta-hydroxylase neurotoxin to selectively induce noradrenergic lesions in the prefrontal cortex or ventral striatum. This work revealed that the integrity of noradrenaline transmission in the ventral striatum is required for the impulsivity-reducing effects of atomoxetine, whereas noradrenergic modulation in the prefrontal cortex is required for top-down control over amphetamine-induced impulsivity (Benn and Robinson 2017).

A subsequent question that then arises is which specific adrenoceptors play a role in impulsivity. In this regard, most recent work has focused on alpha2-adrenoceptors, and few studies have indicated a role for beta-adrenoceptors. Regarding alpha2-adrenoceptors in the brain, these receptors function both as (presynaptic) autoreceptors on noradrenergic cell bodies in the locus coeruleus and on noradrenergic nerve terminals in projection regions and as postsynaptic receptors in target regions such as the prefrontal cortex (for review, see Berridge and Waterhouse 2003). Activation of presynaptic alpha2-adrenoceptors decreases the activity of the noradrenaline system, an effect that is different from activation of postsynaptic alpha2-adrenoceptors. Whereas in vitro or ex vivo assays reveal that alpha2-adrenoceptor ligands might have different affinities for presynaptic or postsynaptic receptors (Molinoff 1984), it is important to keep in mind that it is difficult to truly distinguish presynaptic from postsynaptic effects in systemic behavioural pharmacological studies. Intracranial microinfusions with alpha2-adrenoceptor ligands in selected brain regions, as mentioned above for atomoxetine (Economidou et al. 2012), would be required for to disentangle pre- vs postsynaptic effects of alpha2-adrenoceptor ligands.

Interestingly, in recent years several studies with the alpha2-adrenoceptor antagonist yohimbine have been conducted, showing that this drug increases impulsive action (Adams et al. 2017; Broos et al. 2017; Funk et al. 2019; Mahoney et al. 2016; Sun et al. 2010; Schippers et al. 2016) and reduces impulsive choice in a delay discounting task (Schippers et al. 2016). Moreover, yohimbine was found to attenuate the beneficial effects of the noradrenaline reuptake inhibitor nortriptyline on impulsive action, without having effects by itself (Roychowdhury et al. 2012). This latter observation links activation of postsynaptic alpha2-adrenoceptors to noradrenaline's effects on impulsivity. With regard to its neural site of action, recent work has also shown that microinfusion with yohimbine, but not an alpha-1 or beta-adrenoceptor antagonist, into the orbitofrontal cortex reduces impulsive action (Adams et al. 2017). Whether the effects of yohimbine on impulsivity are purely explained by its actions on noradrenaline transmission is open for further investigation. It would fit with the idea that increased noradrenaline transmission is associated with decreased impulsivity, yet yohimbine also has affinity for several serotonin receptor subtypes as well as the dopamine D2 receptor (Millan et al. 2000), the latter of which has been strongly implicated in impulsivity as discussed earlier in this chapter. Importantly, recent behavioural pharmacological studies have demonstrated that the effects of yohimbine on impulse action are not mediated via interactions with alpha-1 adrenoceptors, corticotropin-releasing factor 1 receptors, dopamine D1/D5 receptors, glucocorticoid receptors and mu-opioid receptors (Mahoney et al. 2016). However, blockade of kappa-opioid receptors attenuated the effects of yohimbine on

impulsive action (Funk et al. 2019), suggesting that yohimbine stimulates release of dynorphin which in turn modulates impulsivity. Taken together, the effects of yohimbine on impulsivity most likely result from a complex interplay between the noradrenergic signaling (most prominently, alpha2-adrenoceptors) and other neurotransmitter systems. Conversely, cocaine-induced increments in impulsive action have also been shown to be attenuated by simultaneous treatment with the alpha2-adrenoceptor agonist guanfacine (Terry et al. 2014), and, more recently, the beneficial effects of atomoxetine on impulsive action were blocked by microinfusions of a dopamine D1/D5 receptor antagonist into the medial prefrontal cortex (Sasamori et al. 2019), further underlining the complex interplay between different neurotransmitter systems in the modulation of impulsivity.

Only a few studies in the last decade have investigated involvement of alpha-1 or beta-adrenoceptors in impulsivity. First, pharmacological challenges with direct alpha-1 or alpha2-adrenoceptor agonists, such as phenylephrine, clonidine and guanfacine, have been shown to be without effect in several studies (Pardey et al. 2013; Van Gaalen et al. 2006b), whereby apparently beneficial effects on impulsivity of these ligands were likely secondary to motor effects (Pattij et al. 2012; Terry et al. 2014). Other studies have reported that treatment with beta-adrenoceptor antagonists such as propranolol was ineffective in modulating impulsive action and impulsive choice (Adams et al. 2017; Mahoney et al. 2016; Milstein et al. 2010; Roychowdhury et al. 2012). This suggests that tonic activation of beta-adrenoceptors is not involved in modulating impulsivity. In contrast, the impulsivity-reducing effects of methylphenidate and nortriptyline could be blocked by propranolol (Milstein et al. 2010; Roychowdhury et al. 2012), suggesting that phasic activation of beta-adrenoceptors does play a role in impulsivity. In support of this, treatment with the selective beta2-adrenoceptor agonist clenbuterol (but not the selective beta1-adrenoceptor agonist dobutamine) was found to reduce impulsive action (Pattij et al. 2012). In the brain, beta2-adrenoceptors are widely expressed in cortical areas, including the prefrontal cortex (Nicholas et al. 1996; Liu et al. 2014), and as such, clenbuterol might shape top-down cortical control (Luo and Zhou 2018).

In sum, studies on the noradrenergic modulation of impulsive behaviour have for the most part focused on alpha2-adrenoceptors. As this noradrenergic receptor subtype can function both as an autoreceptor and as a heteroreceptor, it is important to disentangle whether alpha2-adrenoceptor influence on impulse control is the result of stimulation or inhibition of noradrenergic signaling, the evidence so far pointing towards the former possibility. Future work should be aimed at the identification of the neural sites of action by which alpha2-adrenoceptors regulate impulse control, while the involvement of other adrenoceptor types – which has thus far been much less investigated – should also be assessed in more detail.

3 Novel Targets

It is beyond doubt that neurotransmitter systems other than the monoamine 'usual suspects' play a role in the control of impulsivity. For example, much progress has been made in understanding glutamatergic modulation of impulsive action and impulsive choice. Some interesting observations in this respect include the findings that the metabotropic glutamate receptor 5 (mGluR5) is differentially involved in impulsive action and impulsive choice, as positive allosteric modulation of this receptor reduces impulsive action but does not affect impulsive choice (Isherwood et al. 2015). Also, emphasizing the crosstalk between neurotransmitter systems in modulating impulsivity, it has recently been shown that glutamate-mediated increments in impulsive action could be blocked by treatment with the selective dopamine D2 receptor antagonist eticlopride (Isherwood et al. 2017). This observation reiterates the importance of dopamine D2 receptors as a central mechanism steering impulse control. Since work on the role of glutamate in the modulation of impulse control has been excellently reviewed recently (Carli and Invernizzi 2014; Yates 2018), we now continue with several examples of novel (non-glutamatergic, non-monoaminergic) directions and leads in the pharmacological regulation of impulse control.

First, from a clinical perspective, the opioid system has received a substantial amount of interest as a potential treatment target to ameliorate impulse control in disorders such as behavioural addictions, including pathological gambling, Parkinson's disease and personality disorders. This because in these disorders, the opioid receptor antagonist naltrexone was found to have beneficial therapeutic effects (see e.g. Anderson 2020; Chamberlain and Grant 2019; Goslar et al. 2019; Sgroi and Tonini 2018), which may be (in)directly related to positive effects on impulse control. Preclinical behavioural pharmacological work over the last decade has learned us more about opioid modulation of impulsive behaviour, in terms of subtypes of opioid receptors and brain regions involved. Most studies have demonstrated mu-opioid receptor involvement in impulsive action and impulsive choice, as both acute and subchronic treatments with the mu-opioid receptor agonist morphine were found to increase impulsivity in several translational tasks including the 5-CSRTT, a fixed interval response inhibition task, stop-signal tasks and delay discounting tasks (Harvey-Lewis et al. 2012; Harvey-Lewis and Franklin 2015; Maguire et al. 2016, 2018; Mahoney et al. 2013; Moazen et al. 2018; Pattij et al. 2009). Intracranial microinfusion studies with morphine and DAMGO, a more selective mu-opioid receptor agonist, have pinpointed the prefrontal cortex and nucleus accumbens shell region as candidate brain sites for mu-opioid modulation of impulsivity (Selleck et al. 2015; Wiskerke et al. 2011). In comparison to mu-opioid receptors, kappa-opioid and delta-opioid receptor modulation of impulsivity has been less well documented. Thus, in one study, treatment with a delta-opioid receptor agonist, but not morphine, was found to increase impulsive action in a response inhibition task (Befort et al. 2011). The null effects of morphine in this study seem at odds with the abundant evidence of treatment with this drug increasing

impulsivity. This discrepancy might be explained by methodological characteristics of the response inhibition task used that relied on variable intervals, whereas in a comparable response inhibition task with fixed intervals, morphine did increase impulsive action (Mahoney et al. 2013). Finally, kappa-opioid receptor modulation of impulsivity has also been demonstrated previously. In several studies, systemic injections with the kappa-opioid receptor agonists salvinorin A and U69,593 were found ineffective in affecting impulsive action in the 5-CSRTT (Paine et al. 2007; Nemeth et al. 2010). In contrast, a more recent study did find differential effects of intracerebroventricular administration of the kappa-opioid receptor agonist U50,488 on impulsive action and impulse choice. In a stop-signal task, treatment with U50,488 impaired response inhibition and increased impulsive action, whereas the agonist did not affect impulsive choice in a delay discounting task (Walker and Kissler 2013). Moreover, these effects of U50488 on impulsive action could be blocked by treatment with the noncompetitive kappa-opioid receptor antagonist nor-BNI. These observations are relevant in view of withdrawal-induced increases in dynorphin levels occurring in several substance use disorders, which contributes to the negative emotional symptoms and possibly impulsivity that may precipitate relapse (Zorrilla and Koob 2019). As discussed earlier, resonating well with this idea is the finding that the effects of yohimbine on impulsive action also could be attenuated by nor-BNI (Funk et al. 2019), also suggesting a role for increased dynorphin levels in impulsivity. Not only the interaction with the noradrenaline system is important in how kappa-opioid receptor activation modulates impulsivity. Recent evidence in mice convincingly demonstrates that the impulsivity-inducing effects of a kappa-opioid receptor agonist using a DRL schedule of reinforcement are mediated via dopamine neurons in the ventral tegmental area (Abraham et al. 2018), indicating a dopamine-dependent mechanism. Taken together, the data on delta- and kappa-opioid regulation of impulsive behaviour are equivocal and less clear-cut compared to our understanding of mu-opioid receptors therein. Further work with delta-opioid and kappa-opioid receptor ligands in various tasks is required to better understand the role of these receptors in impulsivity.

To conclude this section, we would like to give two examples of novel leads for targeting impulsivity. Clearly, much more work is needed to firmly establish their involvement in impulsivity, yet they deepen our understanding of the neural underpinnings of impulsive behaviour and may provide new opportunities for therapeutic interventions.

The first example of such a novel target is the ErbB receptor which belongs to a family of tyrosine kinase receptors, which are widely studied in oncology. The neuregulin family includes the endogenous ligands for these receptors; within the central nervous system, these signaling pathways play an important role in neural development, neural circuit assembly, synaptic plasticity and neurotransmission (Mei and Nave 2014). There are at least four different ErbB kinase receptors, ErbB1, ErbB2, ErbB3 and ErbB4 (Birchmeier 2009), and particularly polymorphisms of the neuregulin-ErbB4 signaling pathway have been associated with neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder, bipolar disorders and schizophrenia (Mei and Nave 2014; Pan et al. 2011; Sonuga-Barke

et al. 2008). In support of a role for the neuregulin-ErbB signaling pathway in impulsivity, in the mPFC of mice a quantitative trait locus for impulsivity was identified containing the gene neuregulin 3. Further forward genetic approaches and viral overexpression of neuregulin 3 in the mPFC indicated a causal involvement of this gene in impulsivity as this manipulation selectively increased impulsive action in the 5-CSRTT (Loos et al. 2014). A follow-up study in rats strengthened this observation by demonstrating that pharmacological inhibition of the neuregulin-ErbB signaling pathway by microinfusion of an ErbB inhibitor into the mPFC reduced impulsive action without affecting other behaviours (Loos et al. 2016). Mechanistically, ErbB-mediated modulation of glutamate transmission in the mPFC could be a possible explanation for these effects. Thus, in the mPFC, ErbB activation has been shown to inhibit NMDA receptor signaling by promoting release of GABA from interneurons (Mei and Nave 2014), so that inhibition of ErbB likely has opposite effects to facilitate NMDA receptor-mediated function. Indeed, in support of this, positive allosteric mGluR5 modulation has been found to reduce impulsive action (Isherwood et al. 2015). Alternatively, it has been shown that disruption of neuregulin-ErbB signaling during development leads to elevated striatal dopamine levels (Golani et al. 2014), which could also explain why polymorphisms of these signaling pathways have been associated with neuropsychiatric disorders.

Another example of a recently identified molecule to be involved in impulsivity is *myo*-inositol, which is a membrane lipid and important precursor in the inositol 1,4,5-trisphosphate/calcium (InsP3/Ca2+) signaling pathway. This pathway controls many cellular processes and generates calcium signals required, e.g. contraction in muscle cells, formation of memory in neurons and insulin secretion from the pancreas (Berridge 2009). *Myo*-inositol is also a measurable metabolite in magnetic resonance spectroscopy, and using this approach in rats, it was found that trait high impulsive rats displayed lower *myo*-inositol content in the mPFC compared to low impulsive rats (Jupp et al. 2020). In the same study, ex vivo mass spectroscopy experiments also indicated lower *myo*-inositol levels in high impulsive rats, along with reductions in transcript levels of inositol monophosphatase 1 (IMPase1), a key protein involved in the synthesis of *myo*-inositol. Importantly, in a separate group of rats targeted knockdown of IMPase1 in the mPFC was then found to increase impulsive action, indicating causal involvement of this IMPase1-*myo*-inositol pathway in impulsivity. These data are also relevant from a clinical point of view, since magnetic resonance spectroscopy studies have also reported lower *myo*-inositol levels in the prefrontal cortex in neuropsychiatric disorders, including ADHD (Ferreira et al. 2009), schizophrenia (Das et al. 2018) and substance use disorder (Durazzo et al. 2016). The precise mechanism by which the IMPase1-*myo*-inositol pathway modulates impulsivity needs to be further investigated. Given the fact that the InsP3/Ca2+ pathway is also involved in insulin secretion (Berridge 2009), it is of interest that microinfusions of insulin into the nucleus accumbens were found to reduce impulsive action in the 5-choice serial reaction time task by modulating dopamine transporter function (Schoffelmeer et al. 2011). It is certainly worthwhile to pursue this area of research as it may result in novel targets for therapeutic interventions to ameliorate impulse control disorders.

4 Concluding Remarks

In this chapter, we have summarized recent work on the pharmacological manipulation of impulsive behaviour, using rodent models that align well with laboratory tasks of impulsivity in humans. We have focused on dopaminergic and noradrenergic neurotransmission, both recognized as being important modulator systems of impulse control, as well as several non-monoamine mechanisms that have recently been implicated in impulsivity. In brief, work in the last decade has provided support for a role of dopamine D2 receptors, alpha-adrenoceptors, mu-opioid receptors, the ErbB signaling pathway and *myo*-inositol in impulsive behaviour.

A few points of importance need to be mentioned here. As outlined in the introductory paragraphs of this chapter, impulsivity is a heterogeneous construct. The different subtypes of impulsivity – generally subdivided into impulsive action and impulsive choice – can be studied using dedicated laboratory tasks as described in this chapter. However, we need to keep in mind that the different laboratory tasks used to study impulsive action, e.g. the 5-CSRTT, Go/No go tasks and the stop-signal task, assess distinct, although perhaps overlapping behaviours that may rely on dissociable neural mechanisms. This is important from a psychological, neurobehavioural as well as clinical point of view. That is, different types of mental disorders in which impulsive behaviour plays an important role may be characterized by distinct subtypes of impulsivity, which will likely require precisely targeted pharmacological treatment.

In this chapter we have focused on progress in understanding the neurobiology of impulsive behaviour using translational behavioural pharmacological approaches. We find it heartening to see that in an era where sophisticated modern methods like optogenetics and chemogenetics seem to dominate behavioural neuroscience, many studies remain reliant on 'conventional' pharmacological methods. We believe that true progress lies in using the strengths of both types of approaches. That is, methods like optogenetics and chemogenetics, often combined with the use of genetically engineered rodent lines, can provide knowledge on the neural underpinnings of impulsive behaviour – as well as many other behaviours of course – with unprecedented detail in terms of circuitry, cell-type specificity as well as (in the case of optogenetics) temporal resolution. However, from a clinical perspective these novel techniques are difficult to implement, for example, because they require introduction of exogenous gene products into the brain. In this respect, pharmacological approaches are closer to clinical implementation and do provide valuable insights into the neural and neurochemical basis of impulsivity. Thus, whereas optogenetics and chemogenetics can advance our understanding of the brain, in order for this to find its way into the clinic, it has to be translated into a druggable target. As such, using pharmacological studies of behaviour remains an indispensable approach to deepen our knowledge of the brain and its disorders, including those characterized by impaired impulse control.

References

Abraham AD, Fontaine HM, Song AJ, Andrews MM, Baird MA, Kieffer BL, Land BB, Chavkin C (2018) κ-Opioid receptor activation in dopamine neurons disrupts behavioral inhibition. Neuropsychopharmacology 43:362–372

Adams WK, Barrus MM, Zeeb FD, Cocker PJ, Benoit J, Winstanley CA (2017) Dissociable effects of systemic and orbitofrontal administration of adrenoceptor antagonists on yohimbine-induced motor impulsivity. Behav Brain Res 328:19–27

Anderson G (2020) Pathoetiology and pathophysiology of borderline personality: role of prenatal factors, gut microbiome, mu- and kappa-opioid receptors in amygdala-PFC interactions. Prog Neuro-Psychopharmacol Biol Psychiatry 98:109782

Baarendse PJ, Vanderschuren LJ (2012) Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. Psychopharmacology 219:313–326

Bacqué-Cazenave J, Bharatiya R, Barrière G, Delbecque JP, Bouguiyoud N, Di Giovanni G, Cattaert D, De Deurwaerdère P (2020) Serotonin in animal cognition and behavior. Int J Mol Sci 21:E1649

Bari A, Eagle DM, Mar AC, Robinson ES, Robbins TW (2009) Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. Psychopharmacology 205:273–283

Barlow RL, Gorges M, Wearn A, Niessen HG, Kassubek J, Dalley JW, Pekcec A (2018) Ventral striatal D2/3 receptor availability is associated with impulsive choice behavior as well as limbic corticostriatal connectivity. Int J Neuropsychopharmacol 21:705–715

Befort K, Mahoney MK, Chow C, Hayton SJ, Kieffer BL, Olmstead MC (2011) Effects of delta opioid receptors activation on a response inhibition task in rats. Psychopharmacology 214:967–976

Benn A, Robinson ES (2017) Differential roles for cortical versus sub-cortical noradrenaline and modulation of impulsivity in the rat. Psychopharmacology 234:255–266

Berger SI, Iyengar R (2011) Role of systems pharmacology in understanding drug adverse events. Wiley Interdiscip Rev Syst Biol Med 3:129–135

Berridge MJ (2009) Inositol trisphosphate and calcium signalling mechanisms. Biochim Biophys Acta 1793:933–940

Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Rev 42:33–84

Besson M, Belin D, McNamara R, Theobald DE, Castel A, Beckett VL, Crittenden BM, Newman AH, Everitt BJ, Robbins TW, Dalley JW (2010) Dissociable control of impulsivity in rats by dopamine d2/3 receptors in the core and shell subregions of the nucleus accumbens. Neuropsychopharmacology 35:560–569

Birchmeier C (2009) ErbB receptors and the development of the nervous system. Exp Cell Res 315:611–618

Bizot JC, David S, Trovero F (2011) Effects of atomoxetine, desipramine, d-amphetamine and methylphenidate on impulsivity in juvenile rats, measured in a T-maze procedure. Neurosci Lett 489:20–24

Blondeau C, Dellu-Hagedorn F (2007) Dimensional analysis of ADHD subtypes in rats. Biol Psychiatry 61:1340–1350

Broos N, Schmaal L, Wiskerke J, Kostelijk L, Lam T, Stoop N, Weierink L, Ham J, de Geus EJ, Schoffelmeer AN, van den Brink W, Veltman DJ, de Vries TJ, Pattij T, Goudriaan AE (2012) The relationship between impulsive choice and impulsive action: a cross-species translational study. PLoS One 7:e36781

Broos N, Van Mourik Y, Schetters D, De Vries TJ, Pattij T (2017) Dissociable effects of cocaine and yohimbine on impulsive action and relapse to cocaine seeking. Psychopharmacology 234:3343–3351

Bruinsma B, Terra H, de Kloet SF, Luchicchi A, Timmerman AJ, Remmelink E, Loos M, Pattij T, Mansvelder HD (2019) An automated home-cage-based 5-choice serial reaction time task for rapid assessment of attention and impulsivity in rats. Psychopharmacology 236:2015–2026

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH (2010) Dopaminergic network differences in human impulsivity. Science 329:532

Capecchi MR (2005) Gene targeting in mice: functional analysis of the mammalian genome for the twenty-first century. Nat Rev Genet 6:507–512

Caprioli D, Hong YT, Sawiak SJ, Ferrari V, Williamson DJ, Jupp B, Adrian Carpenter T, Aigbirhio FI, Everitt BJ, Robbins TW, Fryer TD, Dalley JW (2013) Baseline-dependent effects of cocaine pre-exposure on impulsivity and D2/3 receptor availability in the rat striatum: possible relevance to the attention-deficit hyperactivity syndrome. Neuropsychopharmacology 38:1460–1471

Carli M, Invernizzi RW (2014) Serotoninergic and dopaminergic modulation of cortico-striatal circuit in executive and attention deficits induced by NMDA receptor hypofunction in the 5-choice serial reaction time task. Front Neural Circuits 8:58

Carli M, Robbins TW, Evenden JL, Everitt BJ (1983) Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav Brain Res 9:361–380

Carr MR, De Vries TJ, Pattij T (2018) Optogenetic and chemogenetic approaches to manipulate attention, impulsivity and behavioural flexibility in rodents. Behav Pharmacol 29:560–568

Chamberlain SR, Grant JE (2019) Efficacy of pharmacological interventions in targeting decision-making impairments across substance and behavioral addictions. Neuropsychol Rev 29:93–102

Cole BJ, Robbins TW (1987) Amphetamine impairs the discriminative performance of rats with dorsal noradrenergic bundle lesions on a 5-choice serial reaction time task: new evidence for central dopaminergic-noradrenergic interactions. Psychopharmacology 91:458–466

Dalley JW, Robbins TW (2017) Fractionating impulsivity: neuropsychiatric implications. Nat Rev Neurosci 18:158–171

Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Lääne K, Peña Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW (2007) Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315:1267–1270

Das TK, Dey A, Sabesan P, Javadzadeh A, Theberge J, Radua J, Palaniyappan L (2018) Putative astroglial dysfunction in schizophrenia: a meta-analysis of (1)H-MRS studies of medial prefrontal myo-inositol. Front Psych 9:438

Diergaarde L, Pattij T, Poortvliet I, Hogenboom F, de Vries W, Schoffelmeer AN, De Vries TJ (2008) Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. Biol Psychiatry 63:301–308

Durazzo TC, Meyerhoff DJ, Mon A, Abe C, Gazdzinski S, Murray DE (2016) Chronic cigarette smoking in healthy middle- aged individuals is associated with decreased regional brain N-acetylaspartate and glutamate levels. Biol Psychiatry 79:481–488

Eagle DM, Baunez C (2010) Is there an inhibitory-response-control system in the rat? Evidence from anatomical and pharmacological studies of behavioral inhibition. Neurosci Biobehav Rev 34:50–72

Economidou D, Theobald DE, Robbins TW, Everitt BJ, Dalley JW (2012) Norepinephrine and dopamine modulate impulsivity on the five-choice serial reaction time task through opponent actions in the shell and core sub-regions of the nucleus accumbens. Neuropsychopharmacology 37:2057–2066

Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146:348–361

Evenden JL, Ryan CN (1996) The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement. Psychopharmacology 128:161–170

Feola TW, de Wit H, Richards JB (2000) Effects of d-amphetamine and alcohol on a measure of behavioral inhibition in rats. Behav Neurosci 114:838–848

Ferreira PE, Palmini A, Bau CH, Grevet EH, Hoefel JR, Rohde LA, Anes M, Ferreira EE, Belmonte-de-Abreu P (2009) Differentiating attention-deficit/hyperactivity disorder inattentive and combined types: a (1)H-magnetic resonance spectroscopy study of fronto-striato-thalamic regions. J Neural Transm 116:623–629

Funk D, Tamadon S, Coen K, Fletcher PJ, Lê AD (2019) Kappa opioid receptors mediate yohimbine-induced increases in impulsivity in the 5-choice serial reaction time task. Behav Brain Res 359:258–265

Golani I, Tadmor H, Buonanno A, Kremer I, Shamir A (2014) Disruption of the ErbB signaling in adolescence increases striatal dopamine levels and affects learning and hedonic-like behavior in the adult mouse. Eur Neuropsychopharmacol 24:1808–1818

Goslar M, Leibetseder M, Muench HM, Hofmann SG, Laireiter AR (2019) Pharmacological treatments for disordered gambling: a meta-analysis. J Gambl Stud 35:415–445

Harvey-Lewis C, Franklin KB (2015) The effect of acute morphine on delay discounting in dependent and non-dependent rats. Psychopharmacology 232:885–895

Harvey-Lewis C, Perdrizet J, Franklin KB (2012) The effect of morphine dependence on impulsive choice in rats. Psychopharmacology 223:477–487

Heal DJ, Cheetham SC, Smith SL (2009) The neuropharmacology of ADHD drugs in vivo: insights on efficacy and safety. Neuropharmacology 57:608–618

Isherwood SN, Pekcec A, Nicholson JR, Robbins TW, Dalley JW (2015) Dissociable effects of mGluR5 allosteric modulation on distinct forms of impulsivity in rats: interaction with NMDA receptor antagonism. Psychopharmacology 232:3327–3344

Isherwood SN, Robbins TW, Nicholson JR, Dalley JW, Pekcec A (2017) Selective and interactive effects of D2 receptor antagonism and positive allosteric mGluR4 modulation on waiting impulsivity. Neuropharmacology 123:249–260

Jupp B, Caprioli D, Saigal N, Reverte I, Shrestha S, Cumming P, Everitt BJ, Robbins TW, Dalley JW (2013) Dopaminergic and GABA-ergic markers of impulsivity in rats: evidence for anatomical localisation in ventral striatum and prefrontal cortex. Eur J Neurosci 37:1519–1528

Jupp B, Sawiak SJ, van der Veen B, Lemstra S, Toschi C, Barlow RL, Pekcec A, Bretschneider T, Nicholson JR, Robbins TW, Dalley JW (2020) Diminished myoinositol in ventromedial prefrontal cortex modulates the endophenotype of impulsivity. Cereb Cortex. https://doi.org/10.1093/cercor/bhz317

Kabra M, Robie AA, Rivera-Alba M, Branson S, Branson K (2013) JAABA: interactive machine learning for automatic annotation of animal behavior. Nat Methods 10:64–67

Koot S, Adriani W, Saso L, van den Bos R, Laviola G (2009) Home cage testing of delay discounting in rats. Behav Res Methods 41:1169–1176

Kwok R (2019) Deep learning powers a motion-tracking revolution. Nature 574:137–138

Liu Y, Liang X, Ren WW, Li BM (2014) Expression of beta1- and beta2-adrenoceptors in different subtypes of interneurons in the medial prefrontal cortex of mice. Neuroscience 257:149–157

Liu YP, Huang TS, Tung CS, Lin CC (2015) Effects of atomoxetine on attention and impulsivity in the five-choice serial reaction time task in rats with lesions of dorsal noradrenergic ascending bundle. Prog Neuro-Psychopharmacol Biol Psychiatry 56:81–90

Loos M, Pattij T, Janssen MCW, Counotte DS, Schoffelmeer ANM, Smit AB, Spijker S, Van Gaalen MM (2010) Dopamine receptor D1/D5 gene expression in the medial prefrontal cortex predicts impulsive choice in rats. Cereb Cortex 20:1064–1070

Loos M, Mueller T, Gouwenberg Y, Wijnands R, Van der Loo RJ, Neuro-BSIK Mouse Phenomics Consortium, Birchmeier C, Smit AB, Spijker S (2014) Neuregulin-3 in the mouse medial prefrontal cortex regulates impulsive action. Biol Psychiatry 76:648–655

Loos M, Schetters D, Hoogeland M, Spijker S, de Vries TJ, Pattij T (2016) Prefrontal cortical neuregulin-ErbB modulation of inhibitory control in rats. Eur J Pharmacol 781:157–163

Lorbach M, Kyriakou EI, Poppe R, van Dam EA, Noldus LPJJ, Veltkamp RC (2018) Learning to recognize rat social behavior: novel dataset and cross-dataset application. J Neurosci Methods 300:166–172

Luo F, Zhou H (2018) Clenbuterol reduces GABAergic transmission in prefrontal cortex layer 5/6 pyramidal neurons of juvenile rat via reducing action potentials firing frequency of GABAergic interneurons. J Neurochem 144:152–161

Maguire DR, Henson C, France CP (2016) Daily morphine administration increases impulsivity in rats responding under a 5-choice serial reaction time task. Br J Pharmacol 173:1350–1362

Maguire DR, Mendiondo C, France CP (2018) Effects of daily morphine treatment on impulsivity in rats responding under an adjusting stop-signal reaction time task. Behav Pharmacol 29:676–687

Mahoney MK, Silveira MM, Olmstead MC (2013) Increased impulsive action in rats: effects of morphine in a short and long fixed-delay response inhibition task. Psychopharmacology 230:569–577

Mahoney MK, Barnes JH, Wiercigroch D, Olmstead MC (2016) Pharmacological investigations of a yohimbine-impulsivity interaction in rats. Behav Pharmacol 27:585–595

Mazur J (1987) An adjusting procedure for studying delayed reinforcement. In: Commons ML, Nevin JA, Rachlin HC (eds) Quantitative analyses of behaviour: the effect of delay and intervening events on reinforcement value, vol 5. Erlbaum, Hillsdale, pp 55–73

McGuire PS, Seiden LS (1980) The effects of tricyclic antidepressants on performance under a differential-reinforcement-of-low-rates schedule in rats. J Pharmacol Exp Ther 214:635–641

Mei L, Nave KA (2014) Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. Neuron 83:27–49

Millan MJ, Newman-Tancredi A, Audinot V, Cussac D, Lejeune F, Nicolas JP, Cogé F, Galizzi JP, Boutin JA, Rivet JM, Dekeyne A, Gobert A (2000) Agonist and antagonist actions of yohimbine as compared to fluparoxan at alpha(2)-adrenergic receptors (AR)s, serotonin (5-HT)(1A), 5-HT (1B), 5-HT(1D) and dopamine D(2) and D(3) receptors. Significance for the modulation of frontocortical monoaminergic transmission and depressive states. Synapse 35:79–95

Milstein JA, Dalley JW, Robbins TW (2010) Methylphenidate-induced impulsivity: pharmacological antagonism by beta-adrenoreceptor blockade. J Psychopharmacol 24:309–321

Moazen P, Azizi H, Salmanzadeh H, Semnanian S (2018) Adolescent morphine exposure induces immediate and long-term increases in impulsive behavior. Psychopharmacology 235:3423–3434

Molinoff PB (1984) Alpha- and beta-adrenergic receptor subtypes properties, distribution and regulation. Drugs 28(Suppl 2):1–15

Moreno M, Economidou D, Mar AC, López-Granero C, Caprioli D, Theobald DE, Fernando A, Newman AH, Robbins TW, Dalley JW (2013) Divergent effects of $D_{2/3}$ receptor activation in the nucleus accumbens core and shell on impulsivity and locomotor activity in high and low impulsive rats. Psychopharmacology 228:19–30

Navarra R, Graf R, Huang Y, Logue S, Comery T, Hughes Z, Day M (2008) Effects of atomoxetine and methylphenidate on attention and impulsivity in the 5-choice serial reaction time test. Prog Neuro-Psychopharmacol Biol Psychiatry 32:34–41

Nemeth CL, Paine TA, Rittiner JE, Beguin C, Carroll FI, Roth BL et al (2010) Role of kappa-opioid receptors in the effects of salvinorin A and ketamine on attention in rats. Psychopharmacology 210:263–274

Nicholas AP, Hökfelt T, Pieribone VA (1996) The distribution and significance of CNS adrenoceptors examined with in situ hybridization. Trends Pharmacol Sci 17:245–255

Paine TA, Tomasiewicz HC, Zhang K, Carlezon WA (2007) Sensitivity of the five-choice serial reaction time task to the effects of various psychotropic drugs in Sprague–Dawley rats. Biol Psychiatry 62:687–693

Pan B, Huang XF, Deng C (2011) Antipsychotic treatment and neuregulin 1-ErbB4 signalling in schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry 35:924–930

Pardey MC, Kumar NN, Goodchild AK, Cornish JL (2013) Catecholamine receptors differentially mediate impulsive choice in the medial prefrontal and orbitofrontal cortex. J Psychopharmacol 27:203–212

Patel MM, Patel BM (2017) Crossing the blood-brain barrier: recent advances in drug delivery to the brain. CNS Drugs 31:109–133

Paterson NE, Ricciardi J, Wetzler C, Hanania T (2011) Sub-optimal performance in the 5-choice serial reaction time task in rats was sensitive to methylphenidate, atomoxetine and d-amphetamine, but unaffected by the COMT inhibitor tolcapone. Neurosci Res 69:41–50

Pattij T, Vanderschuren LJMJ (2008) The neuropharmacology of impulsive behaviour. Trends Pharmacol Sci 29:192–199

Pattij T, Janssen MC, Vanderschuren LJ, Schoffelmeer AN, van Gaalen MM (2007) Involvement of dopamine D1 and D2 receptors in the nucleus accumbens core and shell in inhibitory response control. Psychopharmacology 191:587–598

Pattij T, Schetters D, Janssen MC, Wiskerke J, Schoffelmeer AN (2009) Acute effects of morphine on distinct forms of impulsive behavior in rats. Psychopharmacology 205:489–502

Pattij T, Schetters D, Schoffelmeer AN, van Gaalen MM (2012) On the improvement of inhibitory response control and visuospatial attention by indirect and direct adrenoceptor agonists. Psychopharmacology 219:327–340

Pezze MA, Dalley JW, Robbins TW (2009) Remediation of attentional dysfunction in rats with lesions of the medial prefrontal cortex by intra-accumbens administration of the dopamine D (2/3) receptor antagonist sulpiride. Psychopharmacology 202:307–313

Rajasethupathy P, Ferenczi E, Deisseroth K (2016) Targeting neural circuits. Cell 165:524–534

Remmelink E, Chau U, Smit AB, Verhage M, Loos M (2017) A one-week 5-choice serial reaction time task to measure impulsivity and attention in adult and adolescent mice. Sci Rep 7:42519

Richards JB, Mitchell SH, de Wit H, Seiden LS (1997) Determination of discount functions in rats with an adjusting-amount procedure. J Exp Anal Behav 67:353–366

Rivalan M, Munawar H, Fuchs A, Winter Y (2017) An automated, experimenter-free method for the standardised, operant cognitive testing of rats. PLoS One 12:e0169476

Robbins TW (2002) The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology 163:362–380

Robinson ES, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, Dalley JW, Robbins TW (2008) Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology 33:1028–1037

Roth BL (2016) DREADDs for neuroscientists. Neuron 89:683–694

Roychowdhury S, Peña-Contreras Z, Tam J, Yadlapalli A, Dinh L, Nichols JA, Basu D, Atzori M (2012) α_2- and β-adrenoceptors involvement in nortriptyline modulation of auditory sustained attention and impulsivity. Psychopharmacology 222:237–245

Sasamori H, Ohmura Y, Yoshida T, Yoshioka M (2019) Noradrenaline reuptake inhibition increases control of impulsive action by activating D(1)-like receptors in the infralimbic cortex. Eur J Pharmacol 844:17–25

Schippers MC, Schetters D, De Vries TJ, Pattij T (2016) Differential effects of the pharmacological stressor yohimbine on impulsive decision making and response inhibition. Psychopharmacology 233:2775–2785

Schoffelmeer AN, Drukarch B, De Vries TJ, Hogenboom F, Schetters D, Pattij T (2011) Insulin modulates cocaine-sensitive monoamine transporter function and impulsive behavior. J Neurosci 31:1284–1291

Selleck RA, Lake C, Estrada V, Redeemer J, Andrzejewski M, Sadeghian K, Baldo BA (2015) Endogenous opioid signaling in the medial prefrontal cortex is required for the expression of hunger-induced impulsive action. Neuropsychopharmacology 40:2464–2474

Sgroi S, Tonini R (2018) Opioidergic modulation of striatal circuits, implications in Parkinson's disease and levodopa induced dyskinesia. Front Neurol 9:524

Simon NW, Gilbert RJ, Mayse JD, Bizon JL, Setlow B (2009) Balancing risk and reward: a rat model of risky decision making. Neuropsychopharmacology 34:2208–2217

Simon NW, Beas BS, Montgomery KS, Haberman RP, Bizon JL, Setlow B (2013) Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. Eur J Neurosci 37:1779–1788

Smith CT, San Juan MD, Dang LC, Katz DT, Perkins SF, Burgess LL, Cowan RL, Manning HC, Nickels ML, Claassen DO, Samanez-Larkin GR, Zald DH (2019) Ventral striatal dopamine transporter availability is associated with lower trait motor impulsivity in healthy adults. Transl Psychiatry 8:269

Sonuga-Barke EJ, Lasky-Su J, Neale BM, Oades R, Chen W, Franke B, Buitelaar J, Banaschewski T, Ebstein R, Gill M, Anney R, Miranda A, Mulas F, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Thompson M, Asherson P, Faraone SV (2008) Does parental expressed emotion moderate genetic effects in ADHD? An exploration using a genome wide association scan. Am J Med Genet B Neuropsychiatr Genet 147B:1359–1368

Sun H, Green TA, Theobald DE, Birnbaum SG, Graham DL, Zeeb FD, Nestler EJ, Winstanley CA (2010) Yohimbine increases impulsivity through activation of cAMP response element binding in the orbitofrontal cortex. Biol Psychiatry 67:649–656

Sun H, Cocker PJ, Zeeb FD, Winstanley CA (2012) Chronic atomoxetine treatment during adolescence decreases impulsive choice, but not impulsive action, in adult rats and alters markers of synaptic plasticity in the orbitofrontal cortex. Psychopharmacology 219:285–301

Terman M, Terman JS (1973) Latency differentiation of hits and false alarms in an operant-psychophysical test. J Exp Anal Behav 20:439–445

Terry AV Jr, Callahan PM, Schade R, Kille NJ, Plagenhoef M (2014) Alpha 2A adrenergic receptor agonist, guanfacine, attenuates cocaine-related impairments of inhibitory response control and working memory in animal models. Pharmacol Biochem Behav 126:63–72

Tsutsui-Kimura I, Ohmura Y, Izumi T, Yamaguchi T, Yoshida T, Yoshioka M (2009) The effects of serotonin and/or noradrenaline reuptake inhibitors on impulsive-like action assessed by the three-choice serial reaction time task: a simple and valid model of impulsive action using rats. Behav Pharmacol 20:474–483

Van Gaalen MM, Brueggeman RJ, Bronius PF, Schoffelmeer AN, Vanderschuren LJ (2006a) Behavioral disinhibition requires dopamine receptor activation. Psychopharmacology 187:73–85

Van Gaalen MM, van Koten R, Schoffelmeer AN, Vanderschuren LJ (2006b) Critical involvement of dopaminergic neurotransmission in impulsive decision making. Biol Psychiatry 60:66–73

Verharen JPH, van den Heuvel MW, Luijendijk M, Vanderschuren LJMJ, Adan RAH (2019) Corticolimbic mechanisms of behavioral inhibition under threat of punishment. J Neurosci 39:435–4364

Walker BM, Kissler JL (2013) Dissociable effects of kappa-opioid receptor activation on impulsive phenotypes in wistar rats. Neuropsychopharmacology 38:2278–2285

Winstanley CA (2011) The utility of rat models of impulsivity in developing pharmacotherapies for impulse control disorders. Br J Pharmacol 164:1301–1321

Winstanley CA, Theobald DE, Dalley JW, Robbins TW (2005) Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulse control disorders. Neuropsychopharmacology 30:669–682

Wiskerke J, Schetters D, van Es IE, van Mourik Y, den Hollander BR, Schoffelmeer AN, Pattij T (2011) μ-Opioid receptors in the nucleus accumbens shell region mediate the effects of amphetamine on inhibitory control but not impulsive choice. J Neurosci 31:262–272

Yates JR (2018) Dissecting drug effects in preclinical models of impulsive choice: emphasis on glutamatergic compounds. Psychopharmacology 235:607–626

Zorrilla EP, Koob GF (2019) Impulsivity derived from the dark side: neurocircuits that contribute to negative urgency. Front Behav Neurosci 13:136

The Neurobiology of Impulsive Decision-Making and Reinforcement Learning in Nonhuman Animals

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Contents

Abstract Impulsive decisions are those that favor immediate over delayed rewards, involve the acceptance of undue risk or uncertainty, or fail to adapt to environmental changes. Pathological levels of impulsive decision-making have been observed in individuals with mental illness, but there may be substantial heterogeneity in the processes that drive impulsive choices. Understanding this behavioral heterogeneity may be critical for understanding associated diverseness in the neural mechanisms that give rise to impulsivity. The application of reinforcement learning algorithms in the deconstruction of impulsive decision-making phenotypes can help bridge the gap between biology and behavior and provide insights into the biobehavioral heterogeneity of impulsive choice. This chapter will review the literature on the neurobiological mechanisms of impulsive decision-making in nonhuman animals; specifically, the role of the amine neuromodulatory systems (dopamine, serotonin,

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norepinephrine, and acetylcholine) in impulsive decision-making and reinforcement learning processes is discussed. Ultimately, the integration of reinforcement learning algorithms with sophisticated behavioral and neuroscience techniques may be critical for advancing the understanding of the neurochemical basis of impulsive decision-making.

Keywords Acetylcholine · Decision making · Dopamine · Impulsivity · Norepinephrine · Reinforcement learning · Serotonin

1 Introduction

Impulsivity has been theorized to be a multidimensional construct and is used to describe a range of behaviors that are poorly conceived, prematurely expressed, unduly risky, and inappropriate to the situation, lack the appropriate foresight and/or deliberation, and typically result in undesirable outcome (Evenden 1999; Whiteside and Lynam 2001; Reynolds et al. 2006). Although the ability to act rapidly or make quick decisions can be advantageous in some circumstances, when these behaviors are persistently expressed and lead to disruptions in normal routines, clinical distress, or adverse consequences, they are considered pathological. Pathological expression of impulsive behaviors has been observed in many psychiatric disorders (Moeller et al. 2001; Swann et al. 2004), including attention deficit hyperactive disorder (Barkley 1997), addiction (Clark et al. 2006; Rogers et al. 2010), and bipolar disorder (Najt et al. 2007), and, consequently, there has been considerable interest in understanding the neurobiology of impulsivity to improve our mechanistic understanding and treatment of these disorders.

Impulsive behaviors are often delineated into three sub-domains: impulsive action, reflection impulsivity, and impulsive choice/decision-making. Impulsive action is used to describe difficulties in inhibiting inappropriate actions, whereas reflection impulsivity is used to describe behaviors that appear to lack foresight and/or deliberation. Impulsive choice/decision-making, which will be the focus of this chapter, is used to describe choices that favor immediate rewards over long-term rewards (e.g., myopic decision-making), involve the acceptance of undue risk or uncertainty (e.g., risky decision-making), or are inflexible to environmental changes (e.g., inflexible decision-making).

Pathological levels of impulsive decision-making have been observed across mental illness (Crean et al. 2000; Itami and Uno 2002; Fishbein et al. 2005; Fillmore and Rush 2006; Wilson et al. 2011), as well as being associated with negative consequences (Aharonovich et al. 2006; Stanger et al. 2012), but there is evidence that myopic, risky, and inflexible decision-making may be independent constructs both at behavioral and neurobiological levels (Peters and Büchel 2009; Dalley and Robbins 2017). For example, individuals with myopic behaviors do not necessarily take more risks or have greater difficulties adapting choices (Fernie et al. 2010; Kjome et al. 2010; Courtney et al. 2012). Decomposing the phenotypic complexity

that underlies impulsive decision-making could be fundamental for developing more effective and individualized treatment strategies for disorders of impulsivity.

Reinforcement learning algorithms have been used to characterize and quantify the computational processes that are performed by the brain to guide decision-making (Dayan and Daw 2008; Lee et al. 2012; Lee 2013). The emerging use of these algorithms in combination with neuroimaging, pharmacology, electrophysiology, and systems-level approaches in animals (Seo et al. 2012; Costa et al. 2015, 2016; Groman et al. 2016, 2019a; Zhukovsky et al. 2019) offers enormous potential for elucidating the biobehavioral processes of decision-making, as well as informing and advancing our understanding of the neurobiology of impulsive decision-making. Deconstructing decision-making – including impulsive decision-making – into simpler, more refined phenotypes with computational approaches that may be more proximally linked to the biology could aid in the identification of novel therapeutic targets for the treatment of disorders of impulsivity (Montague et al. 2012; Wang and Krystal 2014).

This chapter will review the literature on the neurobiology of impulsive decision-making in nonhuman animals within the framework of reinforcement learning. As such, our focus is on measures of impulsive choice/decision-making that have been studied at the neurobiological and computational level. The emphasis on nonhuman animals is driven, in part, by the significant advancements that have been made in the quantification and manipulation of specific neuronal populations, circuits, and signaling pathways in nonhuman animals that have accelerated our mechanistic understanding of impulsive decision-making. First, an overview of the laboratory tasks used for assessing impulsive decision-making in nonhuman animals is provided. A brief description of the reinforcement learning algorithms that are typically used to decompose decision-making phenotypes is then provided in order to evaluate the literature implicating dopamine, serotonin, norepinephrine, and acetylcholine systems in aspects of impulsive decision-making and reinforcement learning. These results are synergized and synthesized to support the argument that reinforcement learning algorithms can provide mechanistic insights into the biological and behavioral heterogeneity of impulsive decision-making that will ultimately be useful for individualized treatment.

1.1 Assessing Impulsive Decision-Making in Nonhuman Animals

Several laboratory tasks have been developed for assessing decision-making in animals. In order to best integrate the human-based findings discussed elsewhere with those described here, we focus on human-based tasks that have been successfully adapted for use in nonhuman animals. Specifically, we delineate decision-making tasks according to the types of impulsive decision-making they are presumed to index, such as choices that occur over delays (myopic decision-making),

choices that occur under risk or uncertainty (risky decision-making), and choices that should optimally adapt to changes in contingencies and/or environment (inflexible decision-making).

1.2 Myopic Decision-Making

A core characteristic of impulsivity is an unusual or extreme propensity for choosing small immediate rewards over larger delayed outcomes, a phenotype that can be quantified in the laboratory using delay discounting (DD) tasks (Kirby and Maraković 1996; Reynolds et al. 2002). In these procedures, subjects are presented with two options that are each associated with variable reward magnitudes (small vs. large) and variable delays to receipt (immediate vs. delayed). When delay is held constant but magnitude is varied, subjects consistently choose the large reward option. However, if a larger reward is received only after a delay, subjects will begin to shift their choices to the immediate, smaller reward. Discounting of rewards as a function of delay can be quantified using hyperbolic models that index the rate at which value declines. High discounting rates indicate that the value of a delayed reward declines faster compared to lower discounting rates.

DD tasks implemented in nonhuman animals are usually administered by systematically varying the delay to the larger reward over blocks of trials. The order of delay presentation (e.g., ascending or descending), however, can impact discounting functions (Tanno et al. 2014). In contrast, procedures that adjust the reward amount or delay duration on a trial-by-trial basis to identify an indifference point, or the point at which choice for the large, delay reward is equivalent to the small, immediate reward, do not suffer from this problem (Richards et al. 1997). Nevertheless, there is evidence that measures derived from DD tasks using adjusting or increasing delays are correlated, suggesting that DD task variants measure the same underlying facet of myopic decision-making (Craig et al. 2014).

1.3 Risky Decision-Making

Many decisions involve a risk of experiencing an adverse consequence, such as loss of a desired outcome or punishment. Several laboratory tasks have been developed to assess risky choice behavior in animals, including the rat Gambling Task (rGT; Zeeb et al. 2009) and a punished risky decision-making task (Simon et al. 2009). In the rGT, rats are presented with multiple choices that differ in the probability and magnitude of rewards and delivery of punishment. Rats must learn to avoid the risky response options, which are associated with larger rewards but more frequent and longer timeout periods. The punished risky decision-making task follows a design similar to that used in DD and the probabilistic discounting tasks; however, instead

of delaying the delivery of the larger reward or increasing uncertainty of reward delivery, choice of the larger reward is probabilistically associated with delivery of an aversive event, such as foot shock (Simon et al. 2009). The probability that the animal will receive a foot shock for choosing the larger reward option increases across blocks of trials to generate risk discounting functions for individual animals: steeper discounting functions indicate greater sensitivity to risk and less risky decision-making.

Choice behavior under conditions where the outcomes are uncertain has also been proposed to index elements of risky decision-making and can be assessed in nonhuman animals using the probabilistic discounting task (St Onge and Floresco 2009). This task requires rats to decide between a small, certain reward and a larger, uncertain reward. The degree of uncertainty for the larger reward is systematically varied across blocks to generate discounting functions similar to those observed using DD tasks. Steeper discounting functions indicate that rats decrease their preference for the larger reward as the likelihood of reward delivery becomes uncertain.

1.4 Inflexible Decision-Making

The ability of animals to adapt their behaviors in response to changing contingencies and/or environments can be assessed using reversal learning tasks (McEnaney and Butter 1969). In this task, subjects are first trained to discriminate between multiple stimuli to obtain a food reward (e.g., S1+, S2−, S3−). Once a performance criterion is met or a certain number of trials are completed, the contingencies are reversed (S1−, S2+, S3−), and the ability of the subject to modify their choices in response to this change is assessed. Difficulties in adjusting behavior following a change in contingencies are considered to be a measure of inflexible decision-making. Many variants of the reversal learning task have been used in animals, including probabilistically vs. deterministically reinforced choices; two- or three-choice tasks; discriminations using visual, spatial, or odor cues; between or within session reversals.

Inflexible decision-making can also be assessed using the recently developed multistage decision-making (MSDM) task. The MSDM task is able to quantify the contributions of retrospective (e.g., model-free) and prospective (e.g., model-based) learning on decision-making in humans (Gläscher et al. 2010; Daw et al. 2011) and has recently been adapted for use in rodents (Miller et al. 2017; Hasz and Redish 2018; Groman et al. 2019b). In the MSDM task, rats make sequential decisions across two stages to obtain a food reward. The choice that the animal makes in the first stage probabilistically determines the choices that the animal can make in the second stage. The impact of model-free and model-based strategies on choice can be quantified by examining how choices are influenced by previous trial events (e.g., choice and outcome) and task structure (e.g., transitions between stages). Although it is not known how these learning strategies relate to measures of impulsivity in

nonhuman animals, self-reported high levels of impulsivity in humans are associated with greater model-free behaviors (Deserno et al. 2015), suggesting that impulsive decision-making may be due to an imbalance in model-free and model-based learning. Only a few studies have examined the neurobiological mechanisms of decision-making in the MSDM task in nonhuman animals (Groman et al. 2019b, c); therefore, subsequent discussions of the MSDM paradigm are necessarily limited.

1.5 Other Laboratory Measures of Impulsivity in Nonhuman Animals

Difficulties inhibiting inappropriate and/or prepotent actions – referred to as impulsive actions – are also prevalent in individuals that self-report high levels of impulsivity (Enticott et al. 2006). Whether impulsive action is related to and/or contributes to impulsive decision-making is not known (Robinson et al. 2009), although there is evidence that the neurobiological mechanisms regulating these forms of impulsivity are, in part, overlapping (for review, see Jentsch et al. 2014). Below, we provide a brief description of the tasks typically used for assessing impulsive action in animals in the following section.

Impulsive action can be assessed in animals using the five-choice serial reaction time (5CSRT; Robbins 2002), the stop-signal reaction time (SSRT; Logan 1994), and the differential reinforcement of low rates (DRL; Seiden et al. 1979) of responding tasks. In the 5CSRT task, animals initiate a trial, and after an inter-trial interval (ITI), a brief visual cue is presented in one of the five options. Animals must choose the correct option to earn a food reward and accuracy of their choices across different visual cue durations providing a measure of attention. Some animals, however, also exhibit high levels of responding during the ITI (referred to as premature responses) that have been equated to the premature, motoric responses that are observed in humans with heightened levels of impulsivity.

The SSRT task, compared to the premature responding in the 5CSRT task, assesses the ability of animals to stop an initiated action (Eagle et al. 2008). Animals are trained to make a motor response following presentation of a go cue in order to receive a food reward delivery. On a subset of trials, however, the go cue is followed by a no-go cue that instructs animals to withhold the response (referred to as the *stop signal*). Animals are able to withhold a majority of responses when the no-go cue is presented immediately following the go cue; however, when presentation of the no-go cue becomes more distal in time from the go cue and more proximal to completion of the motor response, animals have difficulties inhibiting their responses. Most studies using the SSRT task titrate the timing of the stop signal to the delay whereby individuals are able to inhibit 50% of their responses to obtain the SSRT. Animals with low SSRTs have greater difficulty stopping a response, compared to those high SSRTs.

In the DRL task, subjects are required to withhold responding for a fixed period of time whose duration can range anywhere between 10 and 72 s (Seiden et al. 1979). Responses that occur after the withholding period has lapsed are reinforced; however, responses made before the fixed period has ended (e.g., premature responding) result in the trial being reset and are not reinforced. Animals must, therefore, learn to wait to make an appropriate action in the DRL and heightened levels of premature responding thought to reflect a greater degree of impulsive action.

The neurobiology of impulsive action and the biobehavioral overlap with impulsive decision-making has been comprehensively discussed in several review articles (Bari and Robbins 2013; Jentsch et al. 2014; Jupp and Dalley 2014; Dalley and Robbins 2017). Additionally, no studies have used computational approaches to quantify the latent behavioral mechanisms underlying impulsive actions in animals. We chose, therefore, to focus our remaining discussion to studies of impulsive decision-making.

2 Reinforcement Learning Algorithms

Reinforcement learning is an iterative process in which an organism utilizes previous experiences to improve the likelihood that subsequent choices will yield the desired outcome (Lee et al. 2012). Reinforcement learning algorithms provide a framework for understanding how an organism learns a particular action in a specific state of the environment to maximize rewards (Sutton and Barto 1998). These algorithms can index distinct computational steps performed by the organism that would not otherwise be observable or quantifiable by examining gross measures of performance. Value functions in reinforcement learning provide an estimate for the sum of future rewards, and reinforcement learning theory utilizes two different types of value functions: the action value function and the state value function. Action value functions, denoted as *Q(s,a)*, provide an estimate of the sum of future rewards for taking a particular action *(a)* in a particular state *(s)* of the environment. State value functions, denoted as *V(s)*, provide an estimate of the sum of future rewards in a particular state *(s)* of the environment (Lee et al. 2012). Value functions are iteratively updated by individual computational steps, as presented in Fig. 1.

Central to reinforcement learning is the temporal difference signal (δ), which is the learning signal used to update predictions about rewards and actions. A positive temporal difference signal indicates that the reward (r) the organism received was greater than expected or that the state value V(s(t)) was larger than expected. The organism should, therefore, increase the probability of taking the same action when it finds itself in that same state again. In contrast, negative temporal difference signals indicate that the reward or state value was less than expected, and the organism should decrease the probability of repeating the action. The temporal discount signal is modulated by the discount factor (γ) which assigns weights to rewards expected in the future. For example, a discount factor closer to 0 gives more weight to immediate rewards and a discount factor closer to 1 gives more weight to

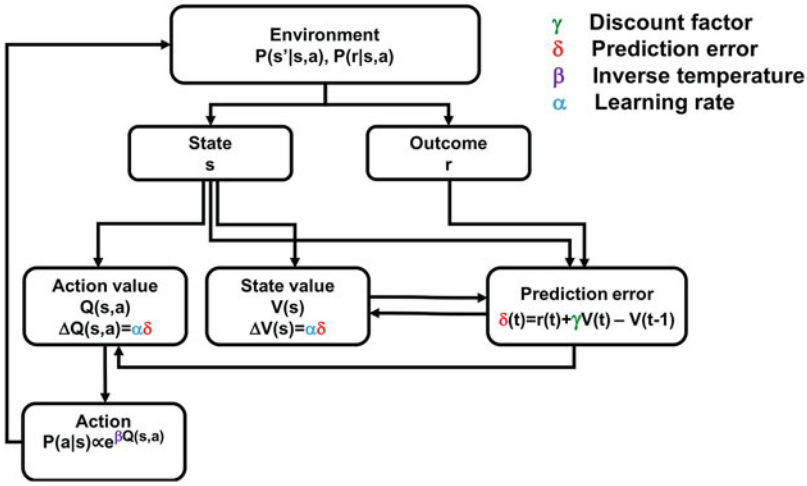

Fig. 1 Diagram of value function updating in a reinforcement learning model. See text for description of each parameter. Figure adapted from Doya (2002)

future, cumulative rewards. Value functions are updated by the temporal difference signal and the learning rate (α) which controls the degree to which the temporal difference signal is incorporated into the value function. Learning rates closer to 1 indicate that learning is occurring quickly as action values are being updated on each trial. In contrast, learning rates closer to 0 indicate that learning is occurring slowly. Action values are converted into probabilities – how likely an agent will select a specific action (P(a|s)) – based on a probability distribution obtained from the softmax function. This function typically includes a parameter known as the inverse temperature (β), which dictates how predictable an action is: large inverse temperature values indicate that actions are less random, and the probability that the animal will select the action with the highest action value moves closer to 1. Smaller inverse temperature values indicate that animals are selecting actions at random (Table 1).

Value functions can be updated by examining how the previous actions and outcomes match the current value function estimate. If the choice outcome experience does not align with what the organism predicted, then the value function needs to be updated. This method is known as model-free updating. A second mechanism for updating value functions is built on associative algorithms whereby an organism uses knowledge of their environment to plan future actions. This mechanism is known as model-based updating (Doya et al. 2002).

Table 1 Examples of common reinforcement-learning parameters, the terminology used to describe these processes and a brief description of what these parameters quantify

Parameter	Terminology	Description
δ	Temporal difference signal	Evaluates whether the outcome/state is better or worse than expected
α	Learning rate	Determines the degree to which the temporal difference signal is incorporated into action value
γ	Discount factor	Assigns weights to future rewards
β	Inverse temperature	Dictates the predictability of an action

3 Neurochemical Mechanisms of Impulsive Decision-Making and Reinforcement Learning

3.1 Dopamine

Dopamine cell bodies are located in the ventral midbrain and in some rostral pontine structures and project to several brain regions, such as the striatum, prefrontal cortex, and amygdala (Fig. 2). There are six major dopaminergic pathways, with the vast majority of studies focusing on the mesocorticolimbic and nigrostriatal pathways.

3.1.1 Myopic Decision-Making

Midbrain dopamine neurons project to many brain regions that have been found to be involved in myopic decision-making, including the striatum (Cardinal et al. 2001), prefrontal cortex, and amygdala. The firing rates of midbrain dopamine neurons and dopamine release in the nucleus accumbens are parametrically modulated by Pavlovian cues that predict delay to reward receipt, and hence value (Kobayashi and Schultz 2008; Saddoris et al. 2015), and studies have demonstrated that optogenetic stimulation that induces dopamine release within the nucleus accumbens reduces discounting functions, such that animals are more tolerant to the delay of the larger reward (Saddoris et al. 2015). Moreover, rats that exhibit steeper discounting functions have a blunted cue dopamine response in a DD task (Moschak and Carelli 2017), and striatal dopamine depletion increases discounting rates (Tedford et al. 2015), suggesting that myopic decision-making may be the result of a hypodopaminergic state.

Pharmacological studies, however, have suggested that dopaminergic signaling mechanisms that influence decision-making in the DD task may vary across different brain regions. Intra-accumbal infusions of D2, but not D1, receptor antagonists increase the discounting rate (Yates and Bardo 2017), whereas D1, but not D2, antagonism in the prefrontal cortex increases the discounting rate (Loos et al. 2010). These functional differences may be linked to the heterogeneity of dopamine receptor expression in cortical compared to subcortical regions.

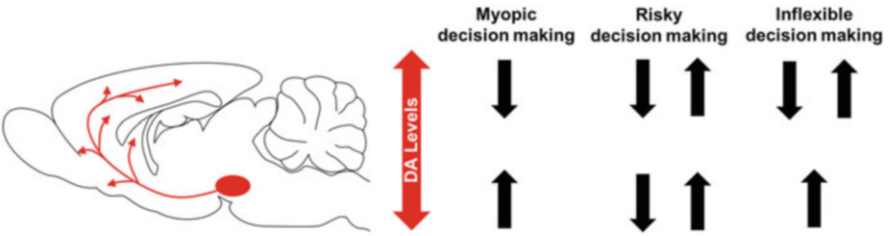

Fig. 2 Distribution of dopamine projections in the rat brain and how modulation of dopamine (DA) signaling impacts myopic, risky, and inflexible decision-making. Upward-facing arrows indicate that impulsive decision-making increases, whereas downward-facing arrows indicate that impulsive decision-making decreases

3.1.2 Risky Decision-Making

Dopamine is also heavily implicated in risky decision-making. Administration of D2-like agonists or amphetamine decreases preference for the large, risky reward under punishment (Simon et al. 2011; Blaes et al. 2018), an effect which is blocked by a D2-like, but not D1-like, receptor antagonist (Simon et al. 2011). Moreover preference for the large, risky reward in the punished risky decision-making task is negatively correlated with striatal D2 receptor expression, and intra-accumbal administration of a D2 agonist has been reported to decrease risk discounting functions (Mitchell et al. 2014). In the rGT, administration of amphetamine shifts responses away from the optimal choice to suboptimal and risky choices, but administration of D1-like and D2-like agonists has no effect (Zeeb et al. 2009). However, administration of D3 receptor agonists has been found to shift responses toward suboptimal and risky choices, whereas antagonism of D3 receptors has the opposite effect (Barrus and Winstanley 2016). Moreover, optogenetic stimulation of D2-expressing neurons in the nucleus accumbens has been reported to reduce risky choices in rats that have high levels of risky decisions (Zalocusky et al. 2016). These findings, collectively, demonstrate a critical role of dopamine in mediating risky decision-making and suggest that dopamine signaling through D2 and D3 receptors may exert opposing effects on risky choices.

Dopamine is also likely involved in decision-making under uncertainty. Administration of amphetamine increases preference for the large, uncertain choice, and this effect is blocked by co-administration of D1 and D2 antagonists (St Onge and Floresco 2009). Moreover, optogenetic stimulation of VTA neurons following uncertain losses increases preference of large, uncertain choices. However, in contrast to decision-making under risk, administration of a D3 agonist, either systemically or directly into the nucleus accumbens, decreases preference for the large, uncertain choice (St Onge and Floresco 2009; Stopper et al. 2013). The divergent role of D3 receptors in decision-making under risk and uncertainty is an area of active research but may be associated with differences in dopaminergic circuits

and/or dynamics that have been observed between the punished decision-making task and probabilistic discounting task.

3.1.3 Inflexible Decision-Making

The ability to adjust behaviors in response to changing contingencies is known to be influenced by dopamine. Depletion of striatal dopamine significantly disrupts the ability of animals to modify their choices following a change in contingencies, but has no effect on their ability to learn a discrimination (O'Neill and Brown 2007; Clarke et al. 2011), suggesting that dopamine may be critically involved in the updating of value representations following a change in stimulus-reward contingencies. Voltammetry studies have found that cue-induced dopamine release is greater following a reversal in animals that learn to adjust their behaviors, but not in animals that fail to do so (Klanker et al. 2015). Thus, difficulties adjusting choices following a reversal may be associated with a hypodopaminergic state. Indeed, low D2/3 receptor availability is associated with poor reversal learning performance (Groman et al. 2011, 2014; Laughlin et al. 2011), and administration of D2/3 antagonists impairs reversal learning performance (Lee et al. 2007; Herold 2010; Groman et al. 2018). However, administration of D2 and D3 agonists has also been found to disrupt reversal learning performance (Boulougouris et al. 2009; Groman et al. 2016), suggesting that the relationship between dopamine and flexible decision-making may be that of an inverted U, where too little or too much dopamine impairs performance. Similar relationships have been observed between dopamine and other cognitive processes (Cools and D'Esposito 2011).

3.1.4 Reinforcement Learning

Midbrain dopamine neuron activity closely resembles the temporal difference error signal: when the outcome is better than expected (e.g., a positive prediction error), dopamine neurons increase their firing, and when the outcome is worse than expected (e.g., a negative prediction error), dopamine neurons decrease their firing (Hollerman and Schultz 1998; Fiorillo et al. 2003). These seminal observations have been recently supported by optogenetic manipulations (Chang et al. 2018) which have artificially manipulated the firing patterns of dopamine neurons to induce prediction errors and assign value onto otherwise neutral cues. Because prediction errors are central to generating accurate action value representations, it is likely that a hypo- or hyper-dopaminergic state can have profound effects on decision-making.

Recent evidence has indicated that dopamine signaling is involved in the integration of prior knowledge into choice (Costa et al. 2015). Indeed, dopaminergic tone in the ventral striatum has been found to correlate with prospective, but not retrospective, learning in rats (Groman et al. 2019b), suggesting that dopamine

signaling in reinforcement learning mechanisms likely extend beyond that of prediction error signaling. As such, this is an area of active investigation in the field of behavioral neuroscience (Keiflin et al. 2019; Sharpe et al. 2017).

3.1.5 Dopamine, Impulsive Decision-Making and Prediction Error

Evidence indicates that high levels of impulsivity are associated with a blunting of the prediction error signal. Self-report measures of impulsivity in humans are associated with lower prediction errors measured with electroencephalogram (Onoda et al. 2010) and negatively related to reward-mediated dopamine release in the nucleus accumbens (Weiland et al. 2014). Furthermore, juveniles with ADHD have blunted prediction error signal in the medial prefrontal cortex, as measured with BOLD and electroencephalogram (Hauser et al. 2014). Rats with steeper discounting functions in the DD task, or rats that do poorly in reversal learning tasks, have also been observed to have reduced dopamine release dynamics (Klanker et al. 2015; Moschak and Carelli 2017). These findings suggest that disruptions in prediction error signaling can manifest as impulsive decision-making. According to the dopamine prediction error theory, animals with blunted dopamine-mediated prediction error signaling would be expected to have corresponding learning deficits; however, this has not been observed (Lee et al. 2007). Disruptions in dopamine signaling that are associated with impulsive decision-making may, therefore, be linked to prospective evaluations, as individuals with pathological gambling disorder have disruptions in the integration of prior knowledge into choice as determined by an optimal Bayesian-derived probability estimate (Lim et al. 2015).

3.2 Serotonin

The neurons of the raphe nuclei are located in the reticular formation of the brain stem and are the primary source of serotonin release in the brain (Fig. 3). There are nine raphe nuclei which project globally throughout the brain.

3.2.1 Myopic Decision-Making

Serotonergic manipulations have been found to have robust effects on myopic decision-making in DD tasks. Selective serotonin reuptake inhibitors (SSRIs) increase selection of larger, delayed rewards (Bizot et al. 1988, 1999), whereas depletion of serotonin results in steeper discounting functions (Bari et al. 2010; however, see Winstanley et al. 2003, 2004). Serotonin efflux in the dorsal raphe nucleus is higher while waiting for delayed rewards (Miyazaki et al. 2011), and optogenetic activation of serotonin neurons in the dorsal raphe nucleus increases the length of time animals are willing to wait for a larger, more certain reward (Miyazaki

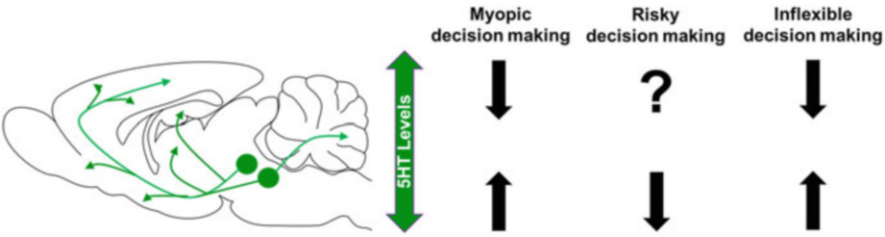

Fig. 3 Distribution of serotonin projections in the rat brain and how modulation of serotonin (5HT) signaling impacts myopic, risky, and inflexible decision-making. Upward-facing arrows indicate that impulsive decision-making increases, whereas downward-facing arrows indicate that impulsive decision-making decreases. A question mark indicates that there is limited or no evidence for the relationship

et al. 2012b, 2014). Serotonin neurons may, therefore, play a critical role in regulating choices in integrating delayed outcomes with previous choices.

3.2.2 Risky Decision-Making

Investigations into the relationship between serotonin and risky decision-making in animals have been limited, although there is evidence in humans to support a relationship (Macoveanu et al. 2013). Systemic reductions in serotonin levels have been found to decrease the preference for the safe option in rat and monkey gambling tasks (Long et al. 2009; Koot et al. 2012). Agonists of 5HT1B receptors have been found to impair decision-making in the rGT, but do not shift choices to the risky option (Zeeb et al. 2009). Infusions of a 5HT1A antagonist into the orbitofrontal cortex (OFC), however, have been found to decrease risk preference, whereas antagonism of 5HT1A receptors in the anterior insular cortex has been reported to increase risk preference (Ishii et al. 2015). Additional studies examining the role of serotonin in punished and probabilistic discounting decision-making tasks are needed to improve our understanding of the likely region- and receptor-specific roles of serotonin in risky decision-making.

3.2.3 Inflexible Decision-Making

Pharmacological manipulations that enhance serotoninergic tone have been found to improve flexible decision-making in reversal learning tasks (Bari et al. 2010; Brigman et al. 2010), whereas depletion of serotonin impairs reversal learning performance (Bari et al. 2010). These effects are likely mediated by prefrontal serotonin signaling as depletion of serotonin in the prefrontal cortex, but not in the striatum, disrupts reversal learning performance (Clarke et al. 2004, 2011). Pharmacological studies have suggested that serotoninergic signaling through 5HT2 receptors is necessary for flexible decision-making. Systemic administration of a 5HT2A

antagonist impairs performance in reversal learning tasks (Alsiö et al. 2015), whereas administration of the 5HT2C antagonist improves reversal learning performance when both given systemically (Boulougouris et al. 2008) and infused directly into the orbitofrontal cortex (Boulougouris and Robbins 2010). These data, taken together, demonstrate that prefrontal serotonergic signaling is critical for engaging in flexible decision-making.

3.2.4 Reinforcement Learning

Serotonin efflux in the dorsal raphe nucleus is higher while waiting for delayed rewards (Miyazaki et al. 2011), and serotonin may be important in controlling the timescale of reward predictions (Schweighofer et al. 2007; Miyazaki et al. 2012a). Phasic activity of midbrain dopamine neurons encodes the prediction error signals that are used to generate value functions. The degree to which these prediction error signals for delayed outcomes are integrated into action values (e.g., the discount rate; γ parameter) is thought to be influenced by serotonin. Recent work has reported that optogenetic stimulation of serotonergic neurons enhances learning over long, but not short, inter-trial intervals (Iigaya et al. 2018), suggesting a role of this neuromodulator system in the integration of extended action-outcome histories into value.

3.2.5 Serotonin, Impulsive Decision-Making and Discount Factor

Decreasing serotonin levels in humans results in steeper discounting functions in a DD task (Crockett et al. 2010) and a lower discounting factor (Schweighofer et al. 2008). Low serotonergic signaling, therefore, may bias individuals to prefer immediate over delayed rewards by altering the timescale of predictions. There is some evidence that this may be specific to punishment of past actions (Tanaka et al. 2009). Moreover, PET neuroimaging studies have found reduced serotonin synthesis in individuals with alcohol use disorder (Nishikawa et al. 2009) and increased serotonin transporter binding in individuals with bipolar disorder (Cannon et al. 2007), both of which have heightened levels of impulsive decision-making compared to controls (Bjork et al. 2004; Dom et al. 2006; Ahn et al. 2011). These data suggest that reduced serotoninergic function may alter the reinforcement learning mechanisms that contribute to impulsive decision-making.

3.3 Norepinephrine

The neurons of the locus coeruleus are located in the pons and are the primary source of norepinephrine input to the forebrain (Fig. 4). However, norepinephrine neurons

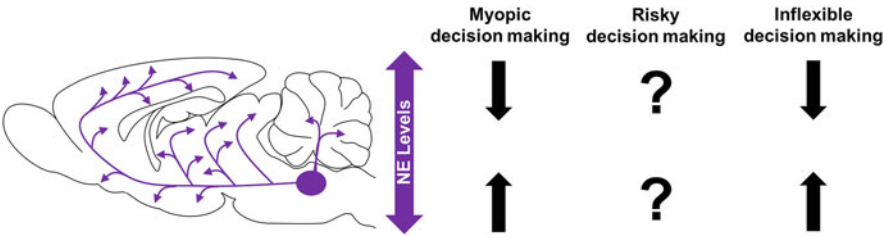

Fig. 4 Distribution of norepinephrine projections in the rat brain and how modulation of norepinephrine (NE) signaling impacts myopic, risky, and inflexible decision-making. Upward-facing arrows indicate that impulsive decision-making increases, whereas downward-facing arrows indicate that impulsive decision-making decreases. A question mark indicates that there is limited or no evidence for the relationship

are also present in the solitary nucleus and medulla. Locus coeruleus neurons send projections broadly throughout the nervous system, including to the spinal cord, brain stem, hypothalamus, and telencephalon.

3.3.1 Myopic Decision-Making

Noradrenergic mechanisms have been implicated in myopic decision-making. Pharmacological increases in extracellular norepinephrine levels by blocking the norepinephrine transporter (NET), which also increases cortical dopamine levels (Bymaster et al. 2002), consistently decrease discounting functions in DD tasks (Robinson et al. 2008; Baarendse and Vanderschuren 2012). These effects appear to be mediated by the α2 adrenergic receptor, as administration of α2 agonists decreases discounting functions (Kim et al. 2012; Nishitomi et al. 2018) and α2 antagonists increases discounting functions (Schippers et al. 2016). Furthermore, intracranial infusions of a α2 agonist into the ventral hippocampus decrease discounting functions (Abela and Chudasama 2014). It is possible that these behavioral effects are, in part, due to changes in dopamine tone, as α2 agonists have been found to decrease dopamine release (Ihalainen and Tanila 2002) possibly through actions downstream of dopamine neurons (Chopin et al. 1999).

3.3.2 Risky Decision-Making

Evidence supporting a role of norepinephrine in risky decision-making in animals is limited. Pharmacological manipulations that increase noradrenergic tone, such as norepinephrine transporter inhibitors, do not alter decision-making in the rGT (Baarendse et al. 2013) or decision-making under punishment (Blaes et al. 2018). However, there is evidence that noradrenergic manipulations alter decision-making in a probabilistic discounting task: the α2 agonist clonidine, but not the agonist guanfacine, decreased the choice of the risky option, whereas the α2 antagonist

yohimbine, which also has affinity for dopaminergic and serotonergic receptors, has the opposite effect (Montes et al. 2015). Given that noradrenergic compounds also impact other neuromodulatory systems – including dopamine and serotonin – additional studies using more select noradrenergic manipulations are needed to determine the role of this system in risky decision-making.

3.3.3 Inflexible Decision-Making

Electrophysiological and pharmacological studies have demonstrated that the noradrenergic system plays a critical role in flexible decision-making. Some of the first evidence came from electrophysiological recordings of locus coeruleus (LC) neurons during a reversal learning task. LC neurons abruptly increase their firing rates following a reversal of contingencies, a signal that preceded any observable behavioral changes (Aston-Jones et al. 1997). Elevations in noradrenergic tone may, therefore, set the stage for behavior to become flexible. Indeed, pharmacological manipulations that increase noradrenergic tone, such as norepinephrine transporter inhibitors, improve the performance of animals in reversal learning tasks (Seu and David Jentsch 2009; Seu et al. 2009). Moreover, α2 agonists have been shown to improve reversal learning performance in older monkeys (Steere and Arnsten 1997). Neurons within the LC project to many regions that are known to be involved in flexible decision-making. Efflux of norepinephrine in the medial prefrontal cortex does not change following a change in contingencies (van der Meulen et al. 2007), suggesting that norepinephrine-mediated enhancements in flexible decision-making may occur in other brain regions, such as the amygdala. Amygdala neurons rapidly adjust their firing rates following a reversal (Paton et al. 2006), a mechanism that may be elicited, in part, by noradrenergic input from LC neurons (Jones and Moore 1977).

3.3.4 Reinforcement Learning

Norepinephrine has been posited to modulate the balance in exploitation and exploration behaviors (Aston-Jones and Cohen 2005), computationally known as the inverse temperature (e.g., β parameter). Neurons within the locus coeruleus rapidly adjust their firing rates when reward contingencies are changed (Aston-Jones et al. 1997; Bouret and Sara 2004), a point when behavior should switch from exploiting the current option to exploring other potentially more valuable options. Phasic firing of neurons in the locus coeruleus is believed to optimize performance in a task (e.g., exploitation), whereas tonic firing is thought to promote disengagement of attention from the current action and redirect attention to other available actions (e.g., exploration; 142).

An alternative theory has been proposed whereby norepinephrine plays a role in learning representations of task states. The ability to modify choice behavior in response to contingency and/or environmental changes, such as in DD and reversal

learning tasks, may depend upon learning representations of different task states, known as "state learning." For example, a choice in one state may yield a desired outcome, but the same choice in another state may not. In order to maximize rewards, the appropriate choice is governed by a representation of the current state. The orbitofrontal cortex has been proposed to be involved in state learning (Wilson et al. 2014), and norepinephrine signaling within the orbitofrontal cortex may mediate the assignment of learning to a new or old associative state (Sadacca et al. 2017).

3.3.5 Norepinephrine, Impulsive Decision-Making and Exploration/ Exploitation

Emerging evidence suggests that impulsivity is associated with biases in the exploit-explore trade-off. Alterations in exploratory behaviors have been observed in disorders associated with high levels of impulsivity, such as ADHD, binge eating disorder, and substance dependence (Kjome et al. 2010; Addicott et al. 2013; Hauser et al. 2014; Morris et al. 2016; Reiter et al. 2017). Decision-making deficits observed in these disorders are improved by noradrenergic compounds, such as the NET inhibitor atomoxetine and the α2 agonist clonidine (Zhang et al. 2012). There is also some evidence that NET availability assessed with a novel PET radioligand is higher in individuals with ADHD compared to controls and is related to genetic as well as epigenetic mechanisms (Sigurdardottir et al. 2016, 2019).

3.4 Acetylcholine

Neurons within the mesopontine tegmentum area, basal nucleus of Meynert, and medial septal nucleus are the primary source of acetylcholine to the central nervous system (Fig. 5). Neurons within the mesopontine tegmentum area send projections to the brainstem, whereas neurons within the nucleus of Meynert and medial septal nucleus send projections to the cerebral cortex, hippocampus, and amygdala (Selden et al. 1998). The principal source of acetylcholine in the striatum, however, comes from cholinergic interneurons that send dense projections to medium spiny neurons (Woolf and Butcher 1981), although recent tracing studies have reported projections from the rostral pedunculopontine nucleus into the striatum (Dautan et al. 2014).

3.4.1 Myopic Decision-Making

Cholinergic modulation of myopic decision-making has not been extensively investigated. Administration of nicotine, which acts as a receptor agonist at most nicotinic acetylcholine (nACh) receptors, decreases the selection of the larger, delayed reward in DD tasks (Kolokotroni et al. 2011). $\alpha_4\beta_2$ nACh receptor density across multiple

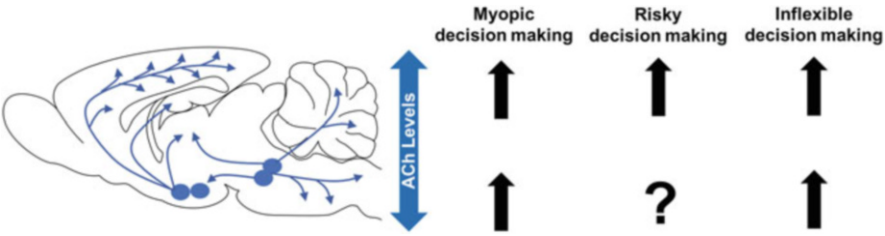

Fig. 5 Distribution of acetylcholine projections in the rat brain and how modulation of acetylcholine (Ach) signaling impacts myopic, risky, and inflexible decision-making. Upward-facing arrows indicate that impulsive decision-making increases, whereas downward-facing arrows indicate that impulsive decision-making decreases. A question mark indicates that there is limited or no evidence for the relationship

cortico-striatal regions is negatively correlated with choice of the larger, delayed reward in a DD task (Mendez et al. 2013), but nicotinic receptor antagonists have not been found to alter choices in DD tasks. Muscarinic receptor antagonists have been found to increase discounting functions (Mendez et al. 2012), suggesting that acetylcholine signaling through muscarinic receptors may modulate myopic decision-making, but additional studies are needed.

3.4.2 Risky Decision-Making

Cholinergic modulation of risky decision-making, similar to myopic decision-making, has not been extensively investigated. Nicotine administration increases the choice of the large, risky reward in the probabilistic discounting task (Mendez et al. 2012), and $\alpha_4\beta_2$ nACh receptor density is negatively correlated with choice of the larger, uncertain reward (Mendez et al. 2013). Administration of muscarinic receptor antagonists disrupts decision-making in the rGT but does not shift responding to the risky choice (Silveira et al. 2015), suggesting that the acetylcholine system may be more involved in learning and/or optimizing choices rather than decision-making under risk.

3.4.3 Inflexible Decision-Making

Lesions of the basal forebrain disrupt serial reversal learning in marmosets (Ridley et al. 1985), suggesting that reductions in cholinergic tone may lead to inflexible decision-making. Pharmacological depletion of cholinergic tone in the striatum disrupts reversal learning (Bradfield et al. 2013), and acetylcholine levels in the striatum increase following a change in contingencies using a place reversal learning task (Ragozzino and Choi 2004; Ragozzino et al. 2009). Blockade of muscarinic, but not nicotinic, receptors in the striatum disrupts reversal performance (Tzavos et al. 2004), and administration of a positive allosteric modulator of muscarinic receptors

improves reversal learning deficits in a transgenic mouse model of Alzheimer's disease (Shirey et al. 2009).

3.4.4 Reinforcement Learning

Acetylcholine has been proposed to facilitate the balance between memory storage and memory renewal (Doya 2002) and may do so through modulation of learning rates (143; e.g., the α parameter). Learning rates control how quickly action values are updated by experience, and acetylcholine release engages neural systems during learning (Gold 2003) with the magnitude of release correlating with measures of memory (McIntyre et al. 2002). It is thought, therefore, that high levels of acetylcholine promote memory storage whereas low levels promote memory renewal (Hasselmo and Bower 1993). Indeed, mice lacking α7 receptors are slower to learn in procedural tasks (Young et al. 2011).

3.4.5 Acetylcholine, Impulsive Decision-Making and Learning Rates

Evidence suggests that decision-making deficits in disorders of impulsivity are associated with disruptions in learning rates. Individuals with pathological gambling and alcohol use disorders report higher levels of impulsivity and are slower to learn following a reversal in contingencies compared to controls (Vanes et al. 2014; Lim et al. 2015). Moreover, rats with steeper discounting functions in the DD task are slower to learn where a hidden platform is located in the Morris water maze (Zaichenko et al. 2017).

4 Summary

Our discussion demonstrates that multiple modulatory systems mediate the expression of impulsive decision-making. We propose that variability in neurotransmitter signaling can lead to the expression of phenotypically different types of impulsive decisions (Fig. 6) that could be useful for developing individualized treatment strategies. For example, treatments that improve dopamine and serotonin signaling may be therapeutically beneficial to individuals who exhibit high levels of risky decision-making, whereas individuals who exhibit pathological levels of myopic decisions may respond better to treatments that improve dopamine, serotonin, and norepinephrine signaling.

5 Conclusions

In this chapter, we have reviewed the role of the neuromodulatory transmitters dopamine, serotonin, norepinephrine, and acetylcholine in impulsive decision-making and reinforcement learning. We provide an integrative framework for

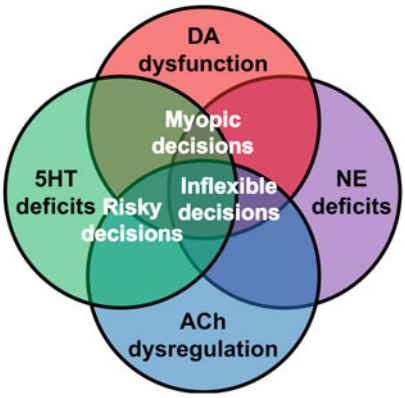

Fig. 6 Diagram for how disruptions in different neuromodulator systems may give rise to different types of impulsive decision-making. Elevations in risky decision-making are associated with dysregulation of dopamine (DA) signaling and increased acetylcholine (ACh) and serotonin (5HT) signaling; elevations in myopic decision-making are associated with reductions in DA, 5HT, and norepinephrine (NE) signaling and dysregulation in ACh signaling; elevations in inflexible decision-making are associated with reductions in 5HT and NE signaling and dysregulation of ACh and DA signaling

understanding how dysfunctional signaling of these neurotransmitter systems can impact select reinforcement learning processes and likely lead to patterns of choice that appear as impulsive (Fig. 7). For example, reduced dopamine-mediated signaling that disrupts prediction error coding and/or prospective planning (e.g., δ parameter) that is used to guide choices could result in deficits in value-based choice behavior. Disruptions in serotoninergic signaling that alter the degree to which future rewards are discounted (e.g., γ parameter) likely decrease the integration of delayed outcomes into action values resulting in myopic choice behavior. An imbalance in cholinergic signaling that alters experience-dependent, action-value updating (e.g., α parameter) could shift the degree to which behavior is flexible or rigid. Reductions in noradrenergic signaling that alter the degree to which individuals explore alternative options (e.g., β parameter) or, possibly, learn about state transitions might result in behavior that is slow to adapt to a change in contingencies. We propose, therefore, that understanding the biology of reinforcement learning processes could improve our understanding of the neurochemical mechanisms that lead to impulsive decision-making in normal and pathological states.

Our discussion, however, does not account for neurochemical interactions or how disruptions across neurotransmitter systems impact decision-making. Our previous work has demonstrated that dopamine and serotonin interact across cortico-striatal regions to guide flexible decision-making (Groman et al. 2013), but how these neurochemical interactions influence specific reinforcement learning processes is not known. Recent advancements in biosensor technology (Marvin et al. 2013; Jing et al. 2018; Sun et al. 2018) may soon enable simultaneous quantification of multiple

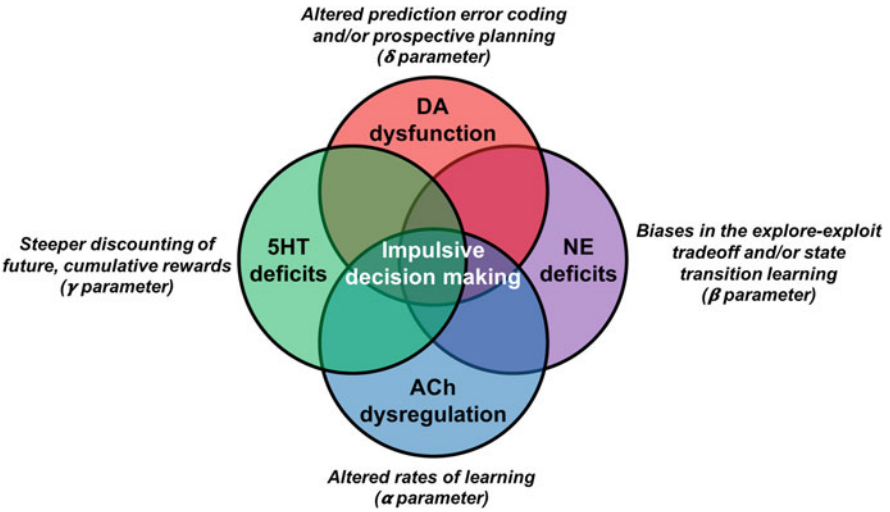

Fig. 7 Diagram for the role of neuromodulatory systems in the reinforcement learning mechanisms that underlie impulsive decision-making

neurotransmitter systems on an unprecedented timescale. Combining this technology with sophisticated behavioral and computational approaches could transform our understanding of how modulatory systems collectively impact neural computations and impulsive decision-making.

In summary, we propose that reinforcement learning algorithms offer a phenotypic bridge between biology and complex behaviors, such as decision-making, that can significantly advance the development of new treatment strategies in individuals with disorders of impulsivity.

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References

Abela AR, Chudasama Y (2014) Noradrenergic α2A-receptor stimulation in the ventral hippocampus reduces impulsive decision-making. Psychopharmacology 231:521–531

Addicott MA, Pearson JM, Wilson J, Platt ML, McClernon FJ (2013) Smoking and the bandit: a preliminary study of smoker and nonsmoker differences in exploratory behavior measured with a multiarmed bandit task. Exp Clin Psychopharmacol 21:66–73

Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV (2006) Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug Alcohol Depend 81:313–322

Ahn W-Y, Rass O, Fridberg DJ, Bishara AJ, Forsyth JK, Breier A, Busemeyer JR, Hetrick WP, Bolbecker AR, O'Donnell BF (2011) Temporal discounting of rewards in patients with bipolar disorder and schizophrenia. J Abnorm Psychol 120:911–921

Alsiö J, Nilsson SRO, Gastambide F, Wang RAH, Dam SA, Mar AC, Tricklebank M, Robbins TW (2015) The role of 5-HT2C receptors in touchscreen visual reversal learning in the rat: a cross-site study. Psychopharmacology 232:4017–4031

Aston-Jones G, Cohen JD (2005) Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. J Comp Neurol 493:99–110

Aston-Jones G, Rajkowski J, Kubiak P (1997) Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. Neuroscience 80:697–715

Baarendse PJJ, Vanderschuren LJMJ (2012) Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. Psychopharmacology 219:313–326

Baarendse PJJ, Winstanley CA, Vanderschuren LJMJ (2013) Simultaneous blockade of dopamine and noradrenaline reuptake promotes disadvantageous decision making in a rat gambling task. Psychopharmacology 225:719–731

Bari A, Robbins TW (2013) Inhibition and impulsivity: behavioral and neural basis of response control. Prog Neurobiol 108:44–79

Bari A, Theobald DE, Caprioli D, Mar AC, Aidoo-Micah A, Dalley JW, Robbins TW (2010) Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learning task in rats. Neuropsychopharmacology 35:1290–1301

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 121:65–94

Barrus MM, Winstanley CA (2016) Dopamine D3 receptors modulate the ability of win-paired cues to increase risky choice in a rat gambling task. J Neurosci 36:785–794

Bizot JC, Thiébot MH, Le Bihan C, Soubrié P, Simon P (1988) Effects of imipramine-like drugs and serotonin uptake blockers on delay of reward in rats. Possible implication in the behavioral mechanism of action of antidepressants. J Pharmacol Exp Ther 246:1144–1151

Bizot J, Le Bihan C, Puech AJ, Hamon M, Thiébot M (1999) Serotonin and tolerance to delay of reward in rats. Psychopharmacology 146:400–412

Bjork JM, Hommer DW, Grant SJ, Danube C (2004) Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1–/type 2–like traits. Alcohol 34:133–150

Blaes SL, Orsini CA, Mitchell MR, Spurrell MS, Betzhold SM, Vera K, Bizon JL, Setlow B (2018) Monoaminergic modulation of decision-making under risk of punishment in a rat model. Behav Pharmacol 29:745–761

Boulougouris V, Robbins TW (2010) Enhancement of spatial reversal learning by 5-HT2C receptor antagonism is neuroanatomically specific. J Neurosci 30:930–938

Boulougouris V, Glennon JC, Robbins TW (2008) Dissociable effects of selective 5-HT2A and 5-HT2C receptor antagonists on serial spatial reversal learning in rats. Neuropsychopharmacology 33:2007–2019

Boulougouris V, Castane A, Robbins TW (2009) Dopamine D2/D3 receptor agonist quinpirole impairs spatial reversal learning in rats: investigation of D3 receptor involvement in persistent behavior. Psychopharmacology 202:611–620

Bouret S, Sara SJ (2004) Reward expectation, orientation of attention and locus coeruleus-medial frontal cortex interplay during learning. Eur J Neurosci 20:791–802

Bradfield LA, Bertran-Gonzalez J, Chieng B, Balleine BW (2013) The thalamostriatal pathway and cholinergic control of goal-directed action: interlacing new with existing learning in the striatum. Neuron 79:153–166

Brigman JL, Mathur P, Harvey-White J, Izquierdo A, Saksida LM, Bussey TJ, Fox S, Deneris E, Murphy DL, Holmes A (2010) Pharmacological or genetic inactivation of the serotonin transporter improves reversal learning in mice. Cereb Cortex 20:1955–1963

Bymaster F, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR, Perry KW (2002) Atomoxetine increases extracellular levels of

norepinephrine and dopamine in prefrontal cortex of rat a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 27:699–711
Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC (2007) Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [11C]DASB; comparison with bipolar disorder. Biol Psychiatry 62:870–877
Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ (2001) Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 292:2499–2501
Chang CY, Gardner MPH, Conroy JC, Whitaker LR, Schoenbaum G (2018) Brief, but not prolonged, pauses in the firing of midbrain dopamine neurons are sufficient to produce a conditioned inhibitor. J Neurosci 38:8822–8830
Chopin P, Colpaert FC, Marien M (1999) Effects of alpha-2 adrenoceptor agonists and antagonists on circling behavior in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal pathway. J Pharmacol Exp Ther 288:798–804
Clark L, Robbins TW, Ersche KD, Sahakian BJ (2006) Reflection impulsivity in current and former substance users. Biol Psychiatry 60:515–522
Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC (2004) Cognitive inflexibility after prefrontal serotonin depletion. Science 304:878–880
Clarke HF, Hill GJ, Robbins TW, Roberts AC (2011) Dopamine, but not serotonin, regulates reversal learning in the marmoset caudate nucleus. J Neurosci 31:4290–4297
Cools R, D'Esposito M (2011) Inverted-U–shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry 69:e113–e125
Costa VD, Tran VL, Turchi J, Averbeck BB (2015) Reversal learning and dopamine: a Bayesian perspective. J Neurosci 35:2407–2416
Costa VD, Dal Monte O, Lucas DR, Murray EA, Averbeck BB (2016) Amygdala and ventral striatum make distinct contributions to reinforcement learning. Neuron 92:505–517
Courtney KE, Arellano R, Barkley-Levenson E, Gálvan A, Poldrack RA, MacKillop J, David Jentsch J, Ray LA (2012) The relationship between measures of impulsivity and alcohol misuse: an integrative structural equation modeling approach. Alcohol Clin Exp Res 36:923–931
Craig AR, Maxfield AD, Stein JS, Renda CR, Madden GJ (2014) Do the adjusting-delay and increasing-delay tasks measure the same construct: delay discounting? Behav Pharmacol 25:306–315
Crean JP, de Wit H, Richards JB (2000) Reward discounting as a measure of impulsive behavior in a psychiatric outpatient population. Exp Clin Psychopharmacol 8:155–162
Crockett MJ, Clark L, Lieberman MD, Tabibnia G, Robbins TW (2010) Impulsive choice and altruistic punishment are correlated and increase in tandem with serotonin depletion. Emotion 10:855–862
Dalley JW, Robbins TW (2017) Fractionating impulsivity: neuropsychiatric implications. Nat Rev Neurosci 18:158–171
Dautan D, Huerta-Ocampo I, Witten IB, Deisseroth K, Bolam JP, Gerdjikov T, Mena-Segovia J (2014) A major external source of cholinergic innervation of the striatum and nucleus accumbens originates in the brainstem. J Neurosci 34:4509–4518
Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ (2011) Model-based influences on humans' choices and striatal prediction errors. Neuron 69:1204–1215
Dayan P, Daw ND (2008) Decision theory, reinforcement learning, and the brain. Cogn Affect Behav Neurosci 8:429–453
Deserno L, Wilbertz T, Reiter A, Horstmann A, Neumann J, Villringer A, Heinze H-J, Schlagenhauf F (2015) Lateral prefrontal model-based signatures are reduced in healthy individuals with high trait impulsivity. Transl Psychiatry 5:e659
Dom G, D'haene P, Hulstijn W, Sabbe B (2006) Impulsivity in abstinent early- and late-onset alcoholics: differences in self-report measures and a discounting task. Addiction 101:50–59

Doya K (2002) Metalearning and neuromodulation. Neural Netw 15:495–506
Doya K, Samejima K, Katagiri K, Kawato M (2002) Multiple model-based reinforcement learning. Neural Comput 14:1347–1369
Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah AP, Robbins TW (2008) Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus. Cereb Cortex 18:178–188
Enticott PG, Ogloff JRP, Bradshaw JL (2006) Associations between laboratory measures of executive inhibitory control and self-reported impulsivity. Personal Individ Differ 41:285–294
Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146:348–361
Fernie G, Cole JC, Goudie AJ, Field M (2010) Risk-taking but not response inhibition or delay discounting predict alcohol consumption in social drinkers. Drug Alcohol Depend 112:54–61
Fillmore MT, Rush CR (2006) Polydrug abusers display impaired discrimination-reversal learning in a model of behavioural control. J Psychopharmacol 20:24–32
Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299:1898–1902
Fishbein DH, Eldreth DL, Hyde C, Matochik JA, London ED, Contoreggi C, Kurian V, Kimes AS, Breeden A, Grant S (2005) Risky decision making and the anterior cingulate cortex in abstinent drug abusers and nonusers. Cogn Brain Res 23:119–136
Gläscher J, Daw N, Dayan P, O'Doherty JP (2010) States versus rewards: dissociable neural prediction error signals underlying model-based and model-free reinforcement learning. Neuron 66:585–595
Gold PE (2003) Acetylcholine modulation of neural systems involved in learning and memory. Neurobiol Learn Mem 80:194–210
Groman SM, Lee B, London ED, Mandelkern MA, James AS, Feiler K, Rivera R, Dahlbom M, Sossi V, Vandervoort E, Jentsch JD (2011) Dorsal striatal D2-like receptor availability covaries with sensitivity to positive reinforcement during discrimination learning. J Neurosci 31:7291–7299
Groman SM, James AS, Seu E, Crawford MA, Harpster SN, Jentsch JD (2013) Monoamine levels within the orbitofrontal cortex and putamen interact to predict reversal learning performance. Biol Psychiatry 73:756–762
Groman SM, James AS, Seu E, Tran S, Clark TA, Harpster SN, Crawford M, Burtner JL, Feiler K, Roth RH, Elsworth JD, London ED, Jentsch JD (2014) In the blink of an eye: relating positive-feedback sensitivity to striatal dopamine D2-like receptors through blink rate. J Neurosci 34:14443–14454
Groman SM, Smith NJ, Petrullli JR, Massi B, Chen L, Ropchan J, Huang Y, Lee D, Morris ED, Taylor JR (2016) Dopamine D3 receptor availability is associated with inflexible decision making. J Neurosci 36:6732–6741
Groman SM, Rich KM, Smith NJ, Lee D, Taylor JR (2018) Chronic exposure to methamphetamine disrupts reinforcement-based decision making in rats. Neuropsychopharmacology 43:770–780
Groman SM, Keistler C, Keip AJ, Hammarlund E, DiLeone RJ, Pittenger C, Lee D, Taylor JR (2019a) Orbitofrontal circuits control multiple reinforcement-learning processes. Neuron 103:734–746.e3
Groman SM, Massi B, Mathias SR, Curry DW, Lee D, Taylor JR (2019b) Neurochemical and behavioral dissections of decision-making in a rodent multistage task. J Neurosci 39:295–306
Groman SM, Massi B, Mathias SR, Lee D, Taylor JR (2019c) Model-free and model-based influences in addiction-related Behaviors. Biol Psychiatry 85:936–945
Hasselmo ME, Bower JM (1993) Acetylcholine and memory. Trends Neurosci 16:218–222
Hasz BM, Redish AD (2018) Deliberation and procedural automation on a two-step task for rats. Front Integr Neurosci 12:30
Hauser TU, Iannaccone R, Ball J, Mathys C, Brandeis D, Walitza S, Brem S (2014) Role of the medial prefrontal cortex in impaired decision making in juvenile attention-deficit/hyperactivity disorder. JAMA Psychiat 71:1165

Herold C (2010) NMDA and D2-like receptors modulate cognitive flexibility in a color discrimination reversal task in pigeons. Behav Neurosci 124:381–390
Hollerman JR, Schultz W (1998) Dopamine neurons report an error in the temporal prediction of reward during learning. Nat Neurosci 1:304–309
Ihalainen JA, Tanila H (2002) In vivo regulation of dopamine and noradrenaline release by α_{2A}-adrenoceptors in the mouse prefrontal cortex. Eur J Neurosci 15:1789–1794
Iigaya K, Fonseca MS, Murakami M, Mainen ZF, Dayan P (2018) An effect of serotonergic stimulation on learning rates for rewards apparent after long intertrial intervals. Nat Commun 9:2477
Ishii H, Ohara S, Tobler PN, Tsutsui K-I, Iijima T (2015) Dopaminergic and serotonergic modulation of anterior insular and orbitofrontal cortex function in risky decision making. Neurosci Res 92:53–61
Itami S, Uno H (2002) Orbitofrontal cortex dysfunction in attention-deficit hyperactivity disorder revealed by reversal and extinction tasks. Neuroreport 13:2453–2457
Jentsch JD, Ashenhurst JR, Cervantes MC, Groman SM, James AS, Pennington ZT (2014) Dissecting impulsivity and its relationships to drug addictions. Ann N Y Acad Sci 1327:1–26
Jing M et al (2018) A genetically encoded fluorescent acetylcholine indicator for in vitro and in vivo studies. Nat Biotechnol 36:726–737
Jones BE, Moore RY (1977) Ascending projections of the locus coeruleus in the rat. II. Autoradiographic study. Brain Res 127:23–53
Jupp B, Dalley JW (2014) Convergent pharmacological mechanisms in impulsivity and addiction: insights from rodent models. Br J Pharmacol 171:4729–4766
Keiflin R, Pribut HJ, Shah NB, Janak PH (2019) Ventral tegmental dopamine neurons participate in reward identity predictions. Curr Biol 29(1):93–103. e3 [Epub ahead of print]
Kim S, Bobeica I, Gamo NJ, Arnsten AFT, Lee D (2012) Effects of α-2A adrenergic receptor agonist on time and risk preference in primates. Psychopharmacology 219:363–375
Kirby KN, Maraković NN (1996) Delay-discounting probabilistic rewards: rates decrease as amounts increase. Psychon Bull Rev 3:100–104
Kjome KL, Lane SD, Schmitz JM, Green C, Ma L, Prasla I, Swann AC, Moeller FG (2010) Relationship between impulsivity and decision making in cocaine dependence. Psychiatry Res 178:299–304
Klanker M, Sandberg T, Joosten R, Willuhn I, Feenstra M, Denys D (2015) Phasic dopamine release induced by positive feedback predicts individual differences in reversal learning. Neurobiol Learn Mem 125:135–145
Kobayashi S, Schultz W (2008) Influence of reward delays on responses of dopamine neurons. J Neurosci 28:7837–7846
Kolokotroni KZ, Rodgers RJ, Harrison AA (2011) Acute nicotine increases both impulsive choice and behavioural disinhibition in rats. Psychopharmacology 217:455–473
Koot S, Zoratto F, Cassano T, Colangeli R, Laviola G, van den Bos R, Adriani W (2012) Compromised decision-making and increased gambling proneness following dietary serotonin depletion in rats. Neuropharmacology 62:1640–1650
Laughlin RE, Grant TL, Williams RW, Jentsch JD (2011) Genetic dissection of behavioral flexibility: reversal learning in mice. Biol Psychiatry 69:1109–1116
Lee D (2013) Decision making: from neuroscience to psychiatry. Neuron 78:233–248
Lee B, Groman S, London ED, Jentsch JD (2007) Dopamine D2/D3 receptors play a specific role in the reversal of a learned visual discrimination in monkeys. Neuropsychopharmacology 32:2125–2134
Lee D, Seo H, Jung MW (2012) Neural basis of reinforcement learning and decision making. Annu Rev Neurosci 35:287–308
Lim MSM, Jocham G, Hunt LT, Behrens TEJ, Rogers RD (2015) Impulsivity and predictive control are associated with suboptimal action-selection and action-value learning in regular gamblers. Int Gambl Stud 15:489–505

Logan GD (1994) On the ability to inhibit thought and action: a users' signal paradigm. - PsycNET. In: Dagenbach D, Carr TH (eds) Inhibitory processes in attention, memory, and language. Academic Press, San Diego

Long AB, Kuhn CM, Platt ML (2009) Serotonin shapes risky decision making in monkeys. Soc Cogn Affect Neurosci 4:346–356

Loos M, Pattij T, Janssen MCW, Counotte DS, Schoffelmeer ANM, Smit AB, Spijker S, Van Gaalen MM (2010) Dopamine receptor D1/D5 gene expression in the medial prefrontal cortex predicts impulsive choice in rats. Cereb Cortex 20:1064–1070

Macoveanu J, Rowe JB, Hornboll B, Elliott R, Paulson OB, Knudsen GM, Siebner HR (2013) Serotonin 2A receptors contribute to the regulation of risk-averse decisions. NeuroImage 83:35–44

Marvin JS, Borghuis BG, Tian L, Cichon J, Harnett MT, Akerboom J, Gordus A, Renninger SL, Chen T-W, Bargmann CI, Orger MB, Schreiter ER, Demb JB, Gan W-B, Hires SA, Looger LL (2013) An optimized fluorescent probe for visualizing glutamate neurotransmission. Nat Methods 10:162–170

McEnaney KW, Butter CM (1969) Perseveration of responding and nonresponding in monkeys with orbital frontal ablations. J Comp Physiol Psychol 68:558–561

McIntyre CK, Pal SN, Marriott LK, Gold PE (2002) Competition between memory systems: acetylcholine release in the hippocampus correlates negatively with good performance on an amygdala-dependent task. J Neurosci 22:1171–1176

Mendez IA, Gilbert RJ, Bizon JL, Setlow B (2012) Effects of acute administration of nicotinic and muscarinic cholinergic agonists and antagonists on performance in different cost–benefit decision making tasks in rats. Psychopharmacology 224:489–499

Mendez IA, Damborsky JC, Winzer-Serhan UH, Bizon JL, Setlow B (2013) $\alpha 4\beta 2*$ and $\alpha 7$ nicotinic acetylcholine receptor binding predicts choice preference in two cost benefit decision-making tasks. Neuroscience 230:121–131

Miller KJ, Botvinick MM, Brody CD (2017) Dorsal hippocampus contributes to model-based planning. Nat Neurosci 20:1269–1276

Mitchell MR, Weiss VG, Beas BS, Morgan D, Bizon JL, Setlow B (2014) Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. Neuropsychopharmacology 39:955–962

Miyazaki KW, Miyazaki K, Doya K (2011) Activation of the central serotonergic system in response to delayed but not omitted rewards. Eur J Neurosci 33:153–160

Miyazaki K, Miyazaki KW, Doya K (2012a) The role of serotonin in the regulation of patience and impulsivity. Mol Neurobiol 45:213–224

Miyazaki KW, Miyazaki K, Doya K (2012b) Activation of dorsal raphe serotonin neurons is necessary for waiting for delayed rewards. J Neurosci 32:10451–10457

Miyazaki KW, Miyazaki K, Tanaka KF, Yamanaka A, Takahashi A, Tabuchi S, Doya K (2014) Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards. Curr Biol 24:2033–2040

Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC (2001) Psychiatric aspects of impulsivity. Am J Psychiatry 158:1783–1793

Montague PR, Dolan RJ, Friston KJ, Dayan P (2012) Computational psychiatry. Trends Cogn Sci 16:72–80

Montes DR, Stopper CM, Floresco SB (2015) Noradrenergic modulation of risk/reward decision making. Psychopharmacology 232:2681–2696

Morris LS, Baek K, Kundu P, Harrison NA, Frank MJ, Voon V (2016) Biases in the explore–exploit tradeoff in addictions: the role of avoidance of uncertainty. Neuropsychopharmacology 41:940–948

Moschak TM, Carelli RM (2017) Impulsive rats exhibit blunted dopamine release dynamics during a delay discounting task independent of cocaine history. eNeuro 4(2):ENEURO.0119-17.2017

Najt P, Perez J, Sanches M, Peluso MAM, Glahn D, Soares JC (2007) Impulsivity and bipolar disorder. Eur Neuropsychopharmacol 17:313–320

Nishikawa M, Diksic M, Sakai Y, Kumano H, Charney D, Palacios-Boix J, Negrete J, Gill K (2009) Alterations in brain serotonin synthesis in male alcoholics measured using positron emission tomography. Alcohol Clin Exp Res 33:233–239

Nishitomi K, Yano K, Kobayashi M, Jino K, Kano T, Horiguchi N, Shinohara S, Hasegawa M (2018) Systemic administration of guanfacine improves food-motivated impulsive choice behavior primarily via direct stimulation of postsynaptic α2A-adrenergic receptors in rats. Behav Brain Res 345:21–29

O'Neill M, Brown VJ (2007) The effect of striatal dopamine depletion and the adenosine A2A antagonist KW-6002 on reversal learning in rats. Neurobiol Learn Mem 88:75–81

Onoda K, Abe S, Yamaguchi S (2010) Feedback-related negativity is correlated with unplanned impulsivity. Neuroreport 21:736–739

Paton JJ, Belova MA, Morrison SE, Salzman CD (2006) The primate amygdala represents the positive and negative value of visual stimuli during learning. Nature 439:865–870

Peters J, Büchel C (2009) Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. J Neurosci 29:15727–15734

Ragozzino ME, Choi D (2004) Dynamic changes in acetylcholine output in the medial striatum during place reversal learning. Learn Mem 11:70–77

Ragozzino ME, Mohler EG, Prior M, Palencia CA, Rozman S (2009) Acetylcholine activity in selective striatal regions supports behavioral flexibility. Neurobiol Learn Mem 91:13–22

Reiter AMF, Heinze H-J, Schlagenhauf F, Deserno L (2017) Impaired flexible reward-based decision-making in binge eating disorder: evidence from computational modeling and functional neuroimaging. Neuropsychopharmacology 42:628–637

Reynolds B, de Wit H, Richards JB (2002) Delay of gratification and delay discounting in rats. Behav Process 59:157–168

Reynolds B, Ortengren A, Richards JB, de Wit H (2006) Dimensions of impulsive behavior: personality and behavioral measures. Personal Individ Differ 40:305–315

Richards JB, Mitchell SH, de Wit H, Seiden LS (1997) Determination of discount functions in rats with an adjusting-amount procedure. J Exp Anal Behav 67:353–366

Ridley RM, Baker HF, Drewett B, Johnson JA (1985) Effects of ibotenic acid lesions of the basal forebrain on serial reversal learning in marmosets. Psychopharmacology 86:438–443

Robbins TW (2002) The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology 163:362–380

Robinson ESJ, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, Dalley JW, Robbins TW (2008) Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology 33:1028–1037

Robinson ESJ, Eagle DM, Economidou D, Theobald DEH, Mar AC, Murphy ER, Robbins TW, Dalley JW (2009) Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: specific deficits in 'waiting' versus 'stopping.'. Behav Brain Res 196:310–316

Rogers RD, Moeller FG, Swann AC, Clark L (2010) Recent research on impulsivity in individuals with drug use and mental health disorders: implications for alcoholism. Alcohol Clin Exp Res 34:1319–1333

Sadacca BF, Wikenheiser AM, Schoenbaum G (2017) Toward a theoretical role for tonic norepinephrine in the orbitofrontal cortex in facilitating flexible learning. Neuroscience 345:124–129

Saddoris MP, Sugam JA, Stuber GD, Witten IB, Deisseroth K, Carelli RM (2015) Mesolimbic dopamine dynamically tracks, and is causally linked to, discrete aspects of value-based decision making. Biol Psychiatry 77:903–911

Schippers MC, Schetters D, De Vries TJ, Pattij T (2016) Differential effects of the pharmacological stressor yohimbine on impulsive decision making and response inhibition. Psychopharmacology 233:2775–2785

Schweighofer N, Tanaka SC, Doya K (2007) Serotonin and the evaluation of future rewards: theory, experiments, and possible neural mechanisms. Ann N Y Acad Sci 1104:289–300

Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, Doya K (2008) Low-serotonin levels increase delayed reward discounting in humans. J Neurosci 28:4528–4532

Seiden LS, Andresen J, MacPhail RC (1979) Methylphenidate and d-amphetamine: effects and interactions with alphamethyltyrosine and tetrabenazine on DRL performance in rats. Pharmacol Biochem Behav 10:577–584

Selden N, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM (1998) Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain 121:2249–2257

Seo M, Lee E, Averbeck BB (2012) Action selection and action value in frontal-striatal circuits. Neuron 74:947–960

Seu E, David Jentsch J (2009) Effect of acute and repeated treatment with desipramine or methylphenidate on serial reversal learning in rats. Neuropharmacology 57:665–672

Seu E, Lang A, Rivera RJ, Jentsch JD (2009) Inhibition of the norepinephrine transporter improves behavioral flexibility in rats and monkeys. Psychopharmacology 202:505–519

Sharpe MJ, Chang CY, Liu MA, Batchelor HM, Mueller LE, Jones JL, Niv Y, Schoenbaum G (2017) Dopamine transients are sufficient and necessary for acquisition of model-based associations. Nat Neurosci 20:735–742

Shirey JK, Brady AE, Jones PJ, Davis AA, Bridges TM, Kennedy JP, Jadhav SB, Menon UN, Xiang Z, Watson ML, Christian EP, Doherty JJ, Quirk MC, Snyder DH, Lah JJ, Levey AI, Nicolle MM, Lindsley CW, Conn PJ (2009) A selective allosteric potentiator of the M1 muscarinic acetylcholine receptor increases activity of medial prefrontal cortical neurons and restores impairments in reversal learning. J Neurosci 29:14271–14286

Sigurdardottir HL, Kranz GS, Rami-Mark C, James GM, Vanicek T, Gryglewski G, Kautzky A, Hienert M, Traub-Weidinger T, Mitterhauser M, Wadsak W, Hacker M, Rujescu D, Kasper S, Lanzenberger R (2016) Effects of norepinephrine transporter gene variants on NET binding in ADHD and healthy controls investigated by PET. Hum Brain Mapp 37:884–895

Sigurdardottir HL, Kranz GS, Rami-Mark C, James GM, Vanicek T, Gryglewski G et al (2019) Association of norepinephrine transporter methylation with in vivo NET expression and hyperactivity–impulsivity symptoms in ADHD measured with PET. Mol Psychiatry:1–10 [Epub ahead of print]

Silveira MM, Malcolm E, Shoaib M, Winstanley CA (2015) Scopolamine and amphetamine produce similar decision-making deficits on a rat gambling task via independent pathways. Behav Brain Res 281:86–95

Simon NW, Gilbert RJ, Mayse JD, Bizon JL, Setlow B (2009) Balancing risk and reward: a rat model of risky decision making. Neuropsychopharmacology 34:2208–2217

Simon NW, Montgomery KS, Beas BS, Mitchell MR, LaSarge CL, Mendez IA, Bañuelos C, Vokes CM, Taylor AB, Haberman RP, Bizon JL, Setlow B (2011) Dopaminergic modulation of risky decision-making. J Neurosci 31:17460–17470

St Onge JR, Floresco SB (2009) Dopaminergic modulation of risk-based decision making. Neuropsychopharmacology 34:681–697

Stanger C, Ryan SR, Fu H, Landes RD, Jones BA, Bickel WK, Budney AJ (2012) Delay discounting predicts adolescent substance abuse treatment outcome. Exp Clin Psychopharmacol 20:205–212

Steere JC, Arnsten AFT (1997) The α-2A noradrenergic receptor agonist guanfacine improves visual object discrimination reversal performance in aged rhesus monkeys. Behav Neurosci 111:883–891

Stopper CM, Khayambashi S, Floresco SB (2013) Receptor-specific modulation of risk-based decision making by nucleus accumbens dopamine. Neuropsychopharmacology 38:715–728

Sun F, Zeng J, Kreitzer AC, Cui G, Correspondence YL (2018) A genetically encoded fluorescent sensor enables rapid and specific detection of dopamine in flies, fish, and mice in brief the development of GPCR-activation-based-DA (GRAB DA) sensors enables measurements of dopamine dynamics in freely behaving animals with high spatiotemporal precision. Cell 174:481–496

Sutton RS, Barto AG (1998) Reinforcement learning: an introduction. MIT Press, Cambridge

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG (2004) Impulsivity: a link between bipolar disorder and substance abuse. Bipolar Disord 6:204–212

Tanaka SC, Shishida K, Schweighofer N, Okamoto Y, Yamawaki S, Doya K (2009) Serotonin affects Association of Aversive outcomes to past actions. J Neurosci 29:15669–15674

Tanno T, Maguire DR, Henson C, France CP (2014) Effects of amphetamine and methylphenidate on delay discounting in rats: interactions with order of delay presentation. Psychopharmacology 231:85–95

Tedford SE, Persons AL, Napier TC (2015) Dopaminergic lesions of the dorsolateral striatum in rats increase delay discounting in an impulsive choice task Finkelstein DI, ed. PLoS One 10: e0122063

Tzavos A, Jih J, Ragozzino ME (2004) Differential effects of M1 muscarinic receptor blockade and nicotinic receptor blockade in the dorsomedial striatum on response reversal learning. Behav Brain Res 154:245–253

van der Meulen JAJ, Joosten RNJMA, de Bruin JPC, Feenstra MGP (2007) Dopamine and noradrenaline efflux in the medial prefrontal cortex during serial reversals and extinction of instrumental goal-directed behavior. Cereb Cortex 17:1444–1453

Vanes LD, van Holst RJ, Jansen JM, van den Brink W, Oosterlaan J, Goudriaan AE (2014) Contingency learning in alcohol dependence and pathological gambling: learning and unlearning reward contingencies. Alcohol Clin Exp Res 38:1602–1610

Wang X-J, Krystal JH (2014) Computational psychiatry. Neuron 84:638–654

Weiland BJ, Heitzeg MM, Zald D, Cummiford C, Love T, Zucker RA, Zubieta J-K (2014) Relationship between impulsivity, prefrontal anticipatory activation, and striatal dopamine release during rewarded task performance. Psychiatry Res Neuroimaging 223:244–252

Whiteside SP, Lynam DR (2001) The five factor model and impulsivity: using a structural model of personality to understand impulsivity. Personal Individ Differ 30:669–689

Wilson VB, Mitchell SH, Musser ED, Schmitt CF, Nigg JT (2011) Delay discounting of reward in ADHD: application in young children. J Child Psychol Psychiatry 52:256–264

Wilson RC, Takahashi YK, Schoenbaum G, Niv Y (2014) Orbitofrontal cortex as a cognitive map of task space. Neuron 81:267–279

Winstanley CA, Dalley JW, Theobald DEH, Robbins TW (2003) Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. Psychopharmacology 170:320–331

Winstanley CA, Dalley JW, Theobald DE, Robbins TW (2004) Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. Neuropsychopharmacology 29:1331–1343

Woolf NJ, Butcher LL (1981) Cholinergic neurons in the caudate-putamen complex proper are intrinsically organized: a combined evans blue and acetylcholinesterase analysis. Brain Res Bull 7:487–507

Yates JR, Bardo MT (2017) Effects of intra-accumbal administration of dopamine and ionotropic glutamate receptor drugs on delay discounting performance in rats. Behav Neurosci 131:392–405

Young JW, Meves JM, Tarantino IS, Caldwell S, Geyer MA (2011) Delayed procedural learning in α7-nicotinic acetylcholine receptor knockout mice. Genes Brain Behav 10:720–733

Zaichenko MI, Bazhenova DA, Grigor'yan GA, Merzhanova GK (2017) Does impulsivity influence the operation of long-term and working memory in rats? Neurosci Behav Physiol 47:427–434

Zalocusky KA, Ramakrishnan C, Lerner TN, Davidson TJ, Knutson B, Deisseroth K (2016) Nucleus accumbens D2R cells signal prior outcomes and control risky decision-making. Nature 531:642–646

Zeeb FD, Robbins TW, Winstanley CA (2009) Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. Neuropsychopharmacology 34:2329–2343

Zhang X-L, Wang G-B, Zhao L-Y, Sun L-L, Wang J, Wu P, Lu L, Shi J (2012) Clonidine improved laboratory-measured decision-making performance in abstinent heroin addicts Zhang XY, ed. PLoS One 7:e29084

Zhukovsky P, Puaud M, Jupp B, Sala-Bayo J, Alsiö J, Xia J, Searle L, Morris Z, Sabir A, Giuliano C, Everitt BJ, Belin D, Robbins TW, Dalley JW (2019) Withdrawal from escalated cocaine self-administration impairs reversal learning by disrupting the effects of negative feedback on reward exploitation: a behavioral and computational analysis. Neuropsychopharmacology 44:2163–2173

Human Brain Imaging Links Dopaminergic Systems to Impulsivity

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Contents

Abstract Molecular and functional imaging techniques have been used and combined with pharmacological probes to evaluate the role of dopamine in impulsivity. Overall, strong evidence links striatal dopaminergic function with impulsivity, measured by self-reports and laboratory tests of cognitive control and reward-based decision-making. The combination of molecular imaging using positron emission tomography (PET) with functional magnetic resonance imaging (fMRI) specifically implicates striatal D2-type dopamine receptors (i.e., D2 and D3) and corticostriatal connectivity in cognitive control. Low levels of striatal and midbrain D2-type receptor availability correlate with self-reported impulsivity, whereas striatal D2-type receptor availability shows positive correlation with motor response inhibition and cognitive flexibility. Impulsive choice on reward-based decision-making tasks also is related to deficits in striatal D2-type dopamine receptor availability, and there is evidence for an inverted U-shaped function in this relationship, reflecting an optimum of striatal dopaminergic activity. Findings from studies of clinical populations that present striatal dopamine D2-type receptor deficits as well

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as healthy control research participants identify D2-type receptors as therapeutic targets to improve cognitive control.

Keywords Cognitive flexibility · D2 receptor · Delay discounting · Functional magnetic resonance imaging · Positron emission tomography · Response inhibition

1 Introduction

Impulsivity is a heterogeneous construct, one facet of which is defined as the propensity to act prematurely or without forethought, substantially influencing a person's success and well-being. It is a prominent feature in neuropsychiatric diseases, including addictions, eating disorders, mood disorders, and attention-deficit hyperactivity disorder (Fenollar-Cortés et al. 2017; McDonald et al. 2019; Patros et al. 2016). In addition, about 14% of patients with Parkinson's disease develop an impulsive-compulsive behavior as an adverse consequence of L-DOPA therapy (Cilia and van Eimeren 2011). As such, impulsivity is an intermediate behavioral phenotype representing a tractable therapeutic target across neuropsychiatric syndromes. With evidence for dopaminergic dysfunction in these disorders (e.g., Belujon and Grace 2017; Chen et al. 2017; Warren et al. 2017), mechanistic studies of the neural basis of impulsivity have taken advantage of molecular and functional brain imaging as well as pharmacological probes in studies of central dopaminergic systems. This review covers those studies with an eye toward how current knowledge can guide the development of new treatments.

2 Measures of Impulsivity in Humans

Trait impulsivity is typically measured using self-report questionnaires. The Barratt Impulsiveness Scale (e.g., Version 11; BIS-11; Patton et al. 1995) is a gold standard for measurement in this domain and has been used extensively in research (see Ireland and Archer 2008; Stanford et al. 2009). Other commonly used inventories are Eysenck's Impulsivity Inventory (Eysenck and Eysenck 1975), which is part of the Eysenck Personality Questionnaire, and the Dickman Impulsivity Inventory (Dickman 1990), which distinguishes between pathological and nonpathological impulsivity. Such measures reflect how a person sees oneself interacting in the world and as such are subject to reporting bias. In addition, other scales, such as the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIPS-RS) (Weintraub et al. 2012), measure medication-induced impulsive-compulsive behaviors, in the domains of pathological gambling, hypersexuality, compulsive shopping, and compulsive eating, as well as medication use and symptoms of obsessive behavior (punding, hobbyism).

In addition to these self-report measures, computerized laboratory tests provide objective measures of cognitive control, which refers to mental processes that modulate other neural systems to maintain goal-directed behavior and counteract impulsive action (Glahn et al. 2016). Go/no go tasks, such as the Stop Signal Task (Logan 1994), measure response inhibition, which is the suppression of actions that are inappropriate in a given context or that interfere with goal-driven behavior (Mostofsky and Simmonds 2008). Overlapping domains include cognitive flexibility, which refers to the readiness with which one can selectively switch between mental processes to produce appropriate behavioral responses (Dajani and Uddin 2015). Behavioral flexibility is the physical manifestation of such switching. Reversal learning tasks, which require choice selection during suppression of previously learned associations, have become the preeminent tests of cognitive flexibility (Izquierdo and Jentsch 2012). Task-switching paradigms and other assessments, such as The Trail Making Test A and B, also provide information about cognitive flexibility (Sanchez-Cubillo et al. 2009).

Decision-making tasks that evaluate impulsive choice are also used in the laboratory. Typically, such tests measure temporal discounting, or the tendency of a person to devalue a reward as function of delay (Bickel and Yi 2008). The steepness of discounting reflects a person's preference for smaller sooner rewards over larger later ones, constituting a form of impatience that leads to suboptimal choice selection. This impatience for receipt of reward can reflect a variety of conditions, including a person's outlook for the future.

As reviewed below, brain imaging has shown associations of central dopaminergic function with self-report measures of impulsivity as well as measures of performance on the aforementioned tests of cognitive control and decision-making. These associations have been demonstrated in healthy research participants as well as samples from clinical populations that show impaired inhibitory control.

3 Impulsivity, Dopamine Receptor Subtypes, and Striatal Dopamine Function

Impulsivity and Dopamine Receptor Subtypes (See Table 1) It is commonly believed that impulsive personality influences the development and maintenance of addiction (Evenden 1999; Ouzir and Errami 2016; Verdejo-García et al. 2008), which in turn is linked to deficits in striatal dopamine D2-type (D2 and D3) receptors (Volkow et al. 2009). A direct link between trait impulsivity and dopamine D2-type receptors appeared in a study of individuals who met criteria for methamphetamine dependence (DSM-IV) and healthy controls (Lee et al. 2009). Recently abstinent methamphetamine-dependent participants scored above controls on all subscales of the BIS-11, and had lower striatal D2-type receptor availability, exhibiting a significant negative relationship between impulsiveness and receptor availability in the caudate nucleus and nucleus accumbens. With data from both groups combined in

Table 1 Human neuroimaging findings linking dopaminergic function in brain to impulsivity

Imaging measure	Impulsivity measure	Research sample	Research findings	Reference
Striatal DA D2-type receptor BP_{ND} (PET, [^{18}F] fallypride)	Impulsive personality (BIS-11 total score)	MA, HC	BIS-11 score correlated negatively with BP_{ND} in caudate and nucleus accumbens in MA group and with BP_{ND} in caudate, putamen/claustrum with groups combined)	Lee et al. (2009)
Ventral striatal DA D2-type receptor BPND (PET, [^{18}F] fallypride)	Impulsive personality (BIS-11 biphasic model: cognitive and behavioral scores)	MA, HC	Group interacted with BP_{ND} on midbrain RSFC: positive association in HC and anticorrelation in MA between ventral striatal BP_{ND} and midbrain RSFC with the striatum, OFC, and insula. Interaction of group with midbrain–left ventral striatum RSFC on cognitive impulsivity: positive association in MA, negative association in HC	Kohno et al. (2016b)
Midbrain DA D2-type receptor BPND (PET, [^{18}F]fallypride)	Impulsive personality: BIS-11 total score	HC	Negative correlation of impulsivity with BP_{ND} and with amphetamine-induced DA release in the striatum	Buckholtz et al. (2010)
Striatal DA D2-type receptor BP_{ND} (PET, [^{18}F] fallypride)	Response inhibition, SSRT	HC	Striatal BP_{ND} was negatively associated with SSRT and positively correlated with inhibition-related fMRI activation in frontostriatal neural circuitry. Correlations were strongest in dorsal striatum	Ghahremani et al. (2012)

(continued)

Table 1 (continued)

Imaging measure	Impulsivity measure	Research sample	Research findings	Reference
Striatal DA D2- and D1-type receptor BP_{ND} (PET, [^{18}F] fallypride and [^{11}C]NNC112)	Response inhibition, (SSRT on Stop-signal task and commission errors on the CPT)	HC	SSRT correlated negatively with both D2- and D1-type DA receptor BP_{ND} values in the dorsal but not the ventral striatum; CPT performance did not correlate with BP_{ND} values	Robertson et al. (2015b)
DA D2-type receptor BP_{ND} in various regions, amphetamine-stimulated striatal DA release (PET, [^{18}F]fallypride)	Cognitive flexibility (task-switching paradigm) and effects of amphetamine	HC	Higher baseline thalamic and cortical BP_{ND} and striatal DA release correlated with greater benefit of amphetamine; striatal DA release partially mediated the association of BP_{ND} with improved flexibility	Samanez-Larkin et al. (2013)
DA synthesis capacity (PET, 6-[^{18}F]fluoro-l-m-tyrosine)	Cognitive flexibility (task-switching paradigm) and functional connectivity (fMRI)	HC (young and older adults)	Low behavioral switch cost correlated with stronger task-related functional connectivity within fronto-striato-thalamic circuits connecting left inferior frontal gyrus, dorsal caudate and ventral lateral/ventral anterior thalamic nuclei. In young adults, functional connectivity mediated the influence of DA synthesis capacity in the dorsal caudate on switch cost. For older adults, dorsal caudate synthesis capacity interacted with connectivity to influence switch cost	Berry et al. (2018)

(continued)

Table 1 (continued)

Imaging measure	Impulsivity measure	Research sample	Research findings	Reference
Striatal DA D2-type receptor BP_{ND} (PET, [^{18}F] fallypride)	Impulsive choice (DDT)	MA	MA displayed steeper temporal discounting and lower striatal BP_{ND} than HC; discount rate correlated negatively with striatal BP_{ND}	Ballard et al. (2015)
Task-based fMRI	Impulsive choice (DDT, probability time trade-off economic model), response to metoclopramide (D2 receptor antagonist)	HC	Metoclopramide reduced temporal discounting over probability and was associated with less activity vs. placebo in the postcentral gyrus as well as frontomedian areas when coding the subjective value	Arrondo et al. (2015)
Striatal DAT (SPECT, [^{123}I] FP-CIT)	PG	PD patients with vs. without PG, HC	Less binding of the radiotracer in PD patients with PG compared to PD patients without PGs	Cilia et al. (2010)
Striatal DAT (SPECT, [^{123}I] FP-CIT)	Diagnosis ICD (pathological gambling, hypersexuality, binge eating, compulsive shopping and/or punding)	PD patients with vs. without ICD	Patients with ICD showed significantly lower DAT binding [mean counts per pixel in the in area of uptake) − (mean counts per pixel in the occipital cortex)]/(mean counts per pixel in the occipital cortex)] in the right striatum with a trend in the left, compared to patients without ICD	Voon et al. (2014)
Striatal DAT (SPECT, [123I] FP-CIT)	Diagnosis of ICD (QUIP-RS, short-form)	PD patients studied at baseline and repeatedly after starting DA	Risk factors for incident ICD symptoms included, greater decrease in right caudate and	Smith et al. (2016)

(continued)

Table 1 (continued)

Imaging measure	Impulsivity measure	Research sample	Research findings	Reference
		replacement therapy	mean striatal DAT availability over the first year, and lower right putamen and mean total striatal DAT availability at any post-baseline visit	
Dopamine synthesis capacity (PET, [^{18}F]DOPA; fMRI, frontostriatal RSFC)	Impulsive-compulsive behavior (QUIP-RS)	PD patients, HC	Severity of impulsive-compulsive behavior correlated with lower DA synthesis capacity in the nucleus accumbens and weaker functional connectivity of the rostral anterior cingulate cortex with the nucleus accumbens	Hammes et al. (2019)
EDVR (PET, [^{18}F]DOPA)	Impulsive personality (BIS-15), impulsive choice (DDT)	HC	Participants with higher baseline EDVR self-reported less impulsivity, and discounted rewards as a function of delay more strongly after receiving L-DOPA; those with lower baseline EDVR self-reported higher impulsivity and exhibited less delay discounting	Petzold et al. (2019b)

BP$_{ND}$ nondisplaceable binding potential, *CPT* continuous performance task, *DA* dopamine, *DDT* delay discounting task, *[^{123}I]FP-CIT* [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane, *EVDR* effective distribution volume ratio of [^{18}F]DOPA influx rate to [^{18}F]DA washout rate, *HC* healthy control, *ICD* impulse control disorder, *MA* methamphetamine-dependent, *[^{11}C]NNC112* 8-chloro-7-hydroxy-3-methyl-5-(7-benzofuranyl)-2,3,4,5-tetrahydro-IH-3-benzazepine, *OFC* orbitofrontal cortex, *PD* Parkinson's disease, *PG* pathological gambling, *QUIP-RS* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale, *RSFC* resting-state functional connectivity, *SPECT* single photon computed tomography, *SSRT* stop-signal reaction time on the Stop Signal Task

voxelwise analyses, impulsivity correlated negatively to dopamine D2-type receptor availability in the left caudate nucleus and right lateral putamen/claustrum, implicating low striatal dopamine D2-type receptor availability as contributing to impulsivity, likely influencing methamphetamine addiction.

Another study evaluated relationships of ventral striatal dopamine D2-type receptor availability to self-reported impulsivity, measured on the BIS-11, and mesocorticolimbic function, indexed by resting-state functional connectivity (RSFC), in methamphetamine-dependent research participants and healthy controls (Kohno et al. 2016b). There was a significant interaction of participant group with ventral striatal dopamine D2-type receptor availability on midbrain connectivity, reflecting a positive relationship in healthy control participants but anticorrelation between ventral striatal receptor availability and RSFC of the midbrain with the striatum, orbitofrontal cortex, and insula in methamphetamine-dependent participants. In addition, methamphetamine-dependent participants exhibited a positive relationship of midbrain–left ventral striatum RSFC with cognitive impulsivity, determined using a bifactor model of the BIS-11 (Reise et al. 2013), whereas healthy controls showed a negative relationship. The results indicated that ventral striatal D2-type receptor signaling might affect system-level activity within the mesocorticolimbic system, possibly explaining high impulsivity in methamphetamine-dependent individuals.

A later study of methamphetamine users replicated the observation of a deficit in striatal D2-type receptor availability relative to controls, but no difference from controls in dopamine D1-type receptor availability (Okita et al. 2018), creating an imbalance in the relative proportions of these two receptor subtypes. Such an imbalance could affect response inhibition and cognitive flexibility, which have been linked to striatal dopamine D2-type receptors (*see below* Ghahremani et al. 2012; Lee et al. 2007). Opposing contributions of D_1- and D_2-mediated dopamine signaling to cognitive function and behavior have been inferred from individual differences in the relationship between the ability to learn from positive and negative feedback with D_1- and D_2-type receptor availabilities, respectively (Cox et al. 2015).

A model of dopamine function in the basal ganglia has been developed on the basis of data from experiments in which dopamine agonist and antagonist drugs were tested for their effects on the expression of instrumental behavior in rodents (Keeler et al. 2014). According to this "prepare and select" model, D_1 receptor activation prepares a set of possible responses and that D_2 receptor activation then functions in selecting the final response. Thus, a relative deficit in D2 relative to D1 signaling may contribute to maladaptive responding on various tasks of cognitive control, including go/no go tasks as well as reversal learning tasks.

These findings in stimulant users may have bearing on other uncontrolled behaviors, such as eating disorders, which also show correlation with deficits in striatal dopamine receptors (Volkow et al. 2017). Methamphetamine-dependent participants residing on a research ward consumed 4,277 $\pm$ 1,121 kcal/day during the first week of hospitalization with no significant decrease in caloric intake during the fourth week (Zorick et al. 2011), suggesting that the hyperphagia reflected more than compensation for the anorectic effects of methamphetamine. This caloric intake

was considerably higher than in hospitalized control subjects (e.g., Perez et al. 2008). Striatal D2-type receptor availability correlated with caloric intake during the first week of abstinence from methamphetamine, and with the increase in BMI over 3 weeks (Zorick et al. 2011). The findings were consistent with the Reward Deficiency Hypothesis, suggesting that the methamphetamine-dependent participants were compensating for deficient striatal dopamine signaling by substituting food as an alternative reward in the absence of their preferred pathological rewarding outlet.

A study of physiologically and psychiatrically healthy adults extended these findings by showing a negative correlation of D2-type dopamine autoreceptor availability in the midbrain with impulsivity measured using the BIS-11 and with amphetamine-induced dopamine release in the striatum (Buckholtz et al. 2010). Impulsivity also correlated positively with amphetamine-induced striatal dopamine release. Path analysis indicated that the negative association of midbrain D2-type dopamine receptor availability on impulsivity was at least partially due to its modulation of striatal dopamine release.

Taken together, these findings in healthy research volunteers and in stimulant users support the view that signaling through D2-type dopamine receptors is important in exerting control over impulsive behavior, likely through effects on corticostriatal circuitry (see Sect. 4 below). Midbrain D2-type autoreceptors limit phasic dopamine release in the striatum, which results in striatal D1 receptor activation in response to environmental stimuli. Based on the view that the basal ganglia contain the direct pathway, activated by D1 receptor to release a motor program, and the indirect pathway, activated by D2 receptor signaling and modulating the response to phasic dopamine release (Grillner and Robertson 2016), a deficit in D2 receptor signaling can promote impulsive behavior.

4 D2-Type Receptors and Inhibitory Control Measured in the Laboratory

Laboratory assessments of task performance, combined with PET and fMRI, have helped elucidate the neurochemical and functional underpinnings of cognitive control (see Table 1). The domains of executive function tested include response inhibition, measured on the Stop Signal Task and Continuous Performance Task, and cognitive flexibility, indexed by performance on a reversal-learning task. Human studies have extended work in animal models and have involved healthy research volunteers as well as chronic methamphetamine users, a clinical group that exhibits greater impulsivity in personality inventories as well as in laboratory tests of inhibitory control, as reviewed below.

Motor Response Inhibition Patients diagnosed with psychiatric disorders that involve impulsive behavior typically exhibit both impaired response inhibition (Aron et al. 2007; Chamberlain and Sahakian 2007; de Wit 2009; Moeller et al.

2001) and dopaminergic dysfunction (Koob and Volkow 2010; Swanson et al. 2007), suggesting that dopamine contributes to response inhibition, but a relationship between response inhibition and dopaminergic neurochemical markers had not been established in humans. Addressing this question, a study was conducted in which healthy research participants underwent PET with [^{18}F]fallypride, a radioligand for dopamine D2-type receptors, and performed the Stop Signal Task during fMRI (Ghahremani et al. 2012). Striatal dopamine D2-type receptor availability correlated negatively with speed of response inhibition (stop-signal reaction time) and positively with inhibition-related fMRI activation in frontostriatal circuitry (Ghahremani et al. 2012). Correlations involving dopamine D2-type receptor availability were strongest in the dorsal regions (caudate and putamen) of the striatum, consistent with findings from lesion and pharmacological studies in rodents suggesting that the nucleus accumbens does not participate in response inhibition as measured by SSRT (Eagle and Robbins 2003; Eagle et al. 2011). The results suggested that striatal D2-like receptor function in humans is important in the neural circuitry that mediates behavioral control, even in the normal nonpathological state.

In another study, response inhibition, indexed by stop-signal reaction time on the Stop Signal task and commission errors on the Continuous Performance task, was examined in relation to striatal D1- and D2-type receptor availability, measured using PET with the ligands [^{11}C]NNC-112 and [^{18}F]fallypride (Robertson et al. 2015b). Stop-signal reaction time showed significant negative correlation with both D1- and D2-type receptor availabilities in the dorsal but not the ventral striatum, whereas performance on the Continuous Performance Task exhibited no correlation with receptor availabilities. Thus, both dopamine receptor subtypes exhibited a role in response inhibition, with the dorsal striatum as an important locus of control. The results were consistent with importance of the balance between phasic and tonic dopaminergic activity, mediated by D1- and D2-type receptors, respectively, in response inhibition. They also suggested that the Stop Signal Task and the Continuous Performance task measure inhibitory control effected by different mechanisms.

Cognitive Flexibility Cognitive flexibility requires inhibition of a learned association so that an organism can adapt its actions to changing reinforcement contingencies in the environment. Lack of such control promotes inflexible, impulsive responding on reversal learning tasks. Studies of rodents and nonhuman primates have demonstrated that dopamine D2-type receptors play a fundamental role in reversal of learned associations (Lee et al. 2007). A recent experiment using mice with a conditional deletion of presynaptic D2 autoreceptors provided evidence that cognitive flexibility involves not only striatopallidal neurons but also presynaptic events involving D2 autoreceptors (Linden et al. 2018). In a dose-response study, infusion of low and high doses of the dopamine D2/3/4 receptor agonist quinpirole into the medial caudate produced a reversal learning deficit in marmosets, whereas intermediate doses produced improvement, consistent with a U-shaped function for dopaminergic involvement (Horst et al. 2019), as evidenced in some human studies of impulsive behaviors (see below). Finally, while most studies did not distinguish between involvement of dopamine D2 and D3 receptors, a role of midbrain D3

receptors was demonstrated using the D3-preferring radioligand [^{11}C]-(+)-propyl-hexahydro-naphtho-oxazin ([^{11}C](+)-PHNO) with PET and a probabilistic discrimination and reversal task in rats (Groman et al. 2016).

Human studies have demonstrated that individuals with certain clinical conditions, such as substance-use disorders that feature dopaminergic neurochemical deficits, also exhibit deficits in cognitive flexibility, which can have negative impact on treatment success. Notably, methamphetamine-dependent individuals have deficits in striatal D2-type receptor and dopamine transporter availabilities (London et al. 2015) as well as in performance in reversal learning (Dean et al. 2011; Ghahremani et al. 2011). Similarly, opioid-dependent patients have longer response times on the Trail Making Task – part A, reflecting impaired capacity for set switching, and striatal dopamine transporter (DAT) availability was negatively correlated with response time, suggesting that lower DAT availability was linked to poorer cognitive flexibility in opioid-dependent patients (Liang et al. 2017).

Studies on the role of dopamine in cognitive flexibility in human subjects have not achieved the level of specificity achieved in the aforementioned animal studies. Specifically, human studies of impulsive behaviors have not distinguished between subpopulations of striatal D2-type receptors localized to different compartments (i.e., pre- vs. postsynaptic) or between dopamine D2 and D3 receptors. Nonetheless, pharmacological and physiological probes, as well as molecular imaging with PET and fMRI have helped clarify the functional neuroanatomy of cognitive flexibility in the human brain. In particular, multi-modal imaging has advanced our understanding of the role of dopamine and thalamocorticostriatal circuitry.

In one study, healthy human participants received oral amphetamine or placebo and performed a task-switching paradigm; baseline dopamine D2-type receptor availability and amphetamine-stimulated dopamine release were measured using [^{18}F]fallypride with PET (Samanez-Larkin et al. 2013). Although most of the participants showed benefits of amphetamine as reductions in switch costs, the effects were variable. Higher baseline thalamic and cortical receptor availability and striatal dopamine release correlated with greater benefit, and striatal dopamine release partially mediated the association of dopamine D2-type receptor availability and improved flexibility. The results pointed to a thalamocorticostriatal network involving stimulant effects on cognitive flexibility and individual differences in the dopamine system influencing the predisposition of a person to experience cognitive benefit from psychostimulants.

Another exemplary study measured dopamine synthesis capacity using PET and 6-[^{18}F]fluoro-l-m-tyrosine and tested for relationships to cognitive flexibility and functional connectivity measured with fMRI (Berry et al. 2018). Cognitive flexibility, measured as low behavioral switch cost in a task-switching paradigm, correlated with stronger task-related functional connectivity within fronto-striato-thalamic circuits connecting left inferior frontal gyrus, dorsal caudate nucleus, and ventral lateral/ventral anterior thalamic nuclei. In young adults, functional connectivity mediated the influence of dopamine synthesis capacity in the dorsal caudate on switch cost. For older adults, dorsal caudate synthesis capacity interacted with

connectivity to influence switch cost. The findings indicated a role of dopamine in tuning striatal circuits to enhance executive function in young adults.

With the advent of targeted brain stimulation techniques, testing the effects of altering activity in a specific brain region can add to knowledge about the functional neuroanatomy of cognitive flexibility. In this regard, a recent study demonstrated that application of cathodal transcranial direct current stimulation to suppress activity of the dorsolateral prefrontal cortex significantly worsened reversal-learning performance, whereas administration of tyrosine, a dopamine precursor, significantly improved performance compared with placebo (Dennison et al. 2019). The findings suggested a causative role for dopamine signaling and dorsolateral prefrontal cortex activity in regulating cognitive flexibility.

5 Dopamine and Impulsive Choice

The discounting of reward value as a function of delay in receipt is a normal behavioral tendency, but when taken to the extreme, it interferes with functioning in daily life and is associated with various maladaptive health behaviors (Gray et al. 2019). Hypersensitivity to delay is a moderately heritable trait and is considered an endophenotype for substance use disorders, attention-deficit hyperactivity disorder, and major depressive disorder (Bickel et al. 2019). Greater delay discounting has also been linked to impulsive choice in studies with laboratory animals, although the effects of dopamine agonists on discounting have been mixed (e.g., Bizot et al. 2007; Cardinal et al. 2000; Floresco et al. 2008; Richards et al. 1999; Wade et al. 2000).

There is also mixed evidence for effects of dopaminergic drugs on impulsive choice in humans. In one study, amphetamine increased delay discounting (de Wit et al. 2002), but in another study, L-DOPA enhanced temporal discounting and its corresponding neural representation in the striatum, measured using fMRI during choice selection (Pine et al. 2010). This difference may reflect the different mechanisms of action of amphetamine and L-DOPA. Among other actions, amphetamine is a monoamine releasing agent, with effects on dopamine, norepinephrine, and, to a lesser extent, serotonin, whereas L-DOPA is a precursor for catecholamines.

Because indirect dopamine receptor agonist drugs can augment transmission at a variety of dopamine receptor subtypes, studies of binding to specific dopamine receptor subtypes provide additional important information (see Table 1). In an exemplary study, individuals with methamphetamine dependence displayed steeper temporal discounting and lower striatal dopamine D2-type receptor availability than controls, and discount rate correlated negatively with striatal receptor availability (Ballard et al. 2015). The results provided the first direct evidence of a link between deficient dopamine D2-type receptor availability and steep temporal discounting.

Although delay discounting often represents a trade-off between time and reward magnitude, other factors can be involved. Another fMRI study of temporal discounting focused on the tradeoff between reward magnitude and outcome probability rather than magnitude (Arrondo et al. 2015). Administration of the dopamine

D2-receptor antagonist metoclopramide to healthy control participants reduced temporal discounting, enhancing the tendency to postpone reward in order to increase the outcome probability. The participants who received metoclopramide presented less modulation in their choices. Medication also was associated with less activity in the postcentral gyrus as well as frontomedian areas when coding the subjective value. Thus, D2 receptors appear to modulate impulsive decision-making by a mechanism that involves limbic associated prefrontal areas in coding the subjective value of options that involve delayed and risky rewards. However, delay and payoff produce activation in thalamus; sensory, parietal, temporal, cingulate, prefrontal, motor, and insular cortices; and basal ganglia, indicating that delay discounting involves a complex interaction of neural systems (Frost and McNaughton 2017).

6 Presynaptic Dopaminergic Markers, Impulsivity, and Reward-Based Decision-Making

The prevalence of the occurrence of an impulsive-compulsive behavior, such as pathological gambling, compulsive shopping, binge eating, or hypersexuality, as an adverse reaction to dopamine replacement therapy, in ~14% of patients with Parkinson's disease (Cilia and van Eimeren 2011), motivated research into the underlying mechanisms. Despite suggestions that this untoward effect reflects a dopaminergic "overdose" in mesocorticolimbic circuits (Cools and Robbins 2004; Voon et al. 2011), molecular imaging findings present a different picture. Studies of Parkinson's disease patients suggest that a presynaptic deficit, specifically low striatal DAT availability, is associated with an increased risk of developing an impulsive compulsive behavior following dopamine replacement therapy (Cilia et al. 2010; Voon et al. 2014; Smith et al. 2016).

Other studies have addressed this question by measuring dopamine synthesis capacity determined using [^{18}F]DOPA with PET (see Table 1). In one such study, patients with Parkinson's disease and healthy controls had impulsive-compulsive behavior quantified on the QUIP-RS questionnaire (Hammes et al. 2019) and frontostriatal resting-state functional connectivity determined using fMRI. The severity of impulsive-compulsive behavior correlated with lower dopamine synthesis capacity in the nucleus accumbens, with weaker functional connectivity of the rostral anterior cingulate cortex with the nucleus accumbens, and with greater cortical thickness of the subgenual rostral anterior cingulate. Thus, reduced dopamine synthesis capacity, but not "dopamine overdose," in the nucleus accumbens and functional as well as structural abnormality in the rostral anterior cingulate cortex, which plays a key role in impulse control, appear to be important risk factors for the development of an impulsive-compulsive behavior following dopamine replacement therapy for Parkinson's disease. Although the exact mechanism by which a presynaptic deficit in dopamine synthesis capacity confers vulnerability to

this untoward effect of medication, a deficit in tonic dopamine release and resulting imbalance in signaling through D2-type vs. D1-type dopamine receptors may be involved.

A more recent report indicated that L-DOPA effects on reward-based decision-making in a randomized, placebo-controlled, double-blind, crossover study were consistent with an inverted U-shaped function whereby both low and high extremes of dopamine signaling were associated with high-impulsive choice. In a population sample, L-DOPA influenced probability discounting for gains in a manner moderated by trait impulsivity (assessed with the BIS-15) (Petzold et al. 2019a). Moreover, changes in performance on delay discounting and mixed gambles tasks depended on trait impulsivity. Participants with low impulsivity discounted rewards as a function of delay more strongly (measured by a delay discounting task), became more risk-seeking for gains (on a probability discounting for gains task), and more loss averse (on a mixed gambles task) after L-DOPA intake, whereas the opposite was exhibited by more-impulsive individuals.

The same investigators followed up that work in an [^{18}F]DOPA PET study in a subset of participants from the original study (Petzold et al. 2019b). The effective distribution volume ratio (EDVR) of [^{18}F]DOPA influx rate to [^{18}F]dopamine washout rate was taken as an index of presynaptic dopaminergic function. Participants with higher baseline EDVR self-reported lower impulsivity, and discounted rewards as a function of delay more strongly after receiving L-DOPA, whereas those with lower baseline EDVR self-reported higher impulsivity and exhibited less delay discounting. These findings support a relationship of striatal dopaminergic activity to trait impulsivity and endorse the notion that there is a nonlinear, possibly inverted U-shaped, relationship between striatal dopaminergic function and delay discounting.

Studies of laboratory animals and of human volunteers have provided evidence for an inverted U-shaped relationship between dopaminergic function and cognitive performance. Reminiscent of findings with L-DOPA and measures of impulsive choice are the effects of bromocriptine on working memory. Healthy individuals with low dopamine synthesis capacity exhibited improved performance, but those with high baseline synthesis capacity exhibited impairment after receiving bromocriptine (Cools et al. 2008). In addition, a study of healthy participants who performed a reward-based decision-making task indicated that prefrontal cortical function and choice selection vary as a function of dopamine signaling capacity assessed using a composite genotype score considering functional variation across five genes that influence dopaminergic signaling (Kohno et al. 2016a). The gene score exhibited a quadratic relationship with decision-making performance, consistent with an inverted U-shaped relationship of dopaminergic function with behavior.

7 Summary and Future Directions

Substantial experimental evidence points to an important role of dopaminergic transmission, and especially dopamine D2-type receptors and limbic cortical circuitry, in influencing impulsivity. Relevant studies include administration of indirect dopaminergic receptor agonists and selective dopamine receptor antagonists, molecular imaging of pre- and postsynaptic dopaminergic neurochemical markers, and fMRI paired with behavioral assessments. Human investigations have taken advantage of fMRI and multi-modal imaging to link neurochemical markers with measures of activity in regions and neural circuits. Yet they have lagged behind animal studies in isolating contributions of subpopulations of D2 receptors and separating involvement of D2 vs. D3 dopamine receptors, which differ in function.

Existing evidence calls for approaches to increase signaling through D2-type receptors. Given the differential distributions and functions of dopamine receptor subtypes in the brain, pharmacological approaches aimed at altering the balance between signaling at these subtypes might ameliorate impulsive behaviors associated with addictions and other neuropsychiatric disorders. Ongoing work is evaluating pharmacological approaches to increasing the densities of striatal D2-type dopamine receptors indirectly, following demonstrations of such upregulation in rodents with varenicline (Crunelle et al. 2011, 2012). In addition, non-pharmacological means, such as exercise training, which upregulates striatal dopamine D2-type receptors in methamphetamine users (Robertson et al. 2015a), offers some promise. Other pharmacological approaches might include D3 receptor antagonist drugs (Cortés et al. 2016; Paterson et al. 2014) and efforts to develop selective D1 receptor antagonists (Arnsten et al. 2017).

References

Arnsten AF, Girgis RR, Gray DL, Mailman RB (2017) Novel dopamine therapeutics for cognitive deficits in schizophrenia. Biol Psychiatry 81:67–77

Aron AR, Durston S, Eagle DM, Logan GD, Stinear CM, Stuphorn V (2007) Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. J Neurosci 27:11860–11864

Arrondo G, Aznárez-Sanado M, Fernández-Seara MA, Goñi J, Loayza FR, Salamon-Klobut E, Heukamp FH, Pastor MA (2015) Dopaminergic modulation of the trade-off between probability and time in economic decision-making. Eur Neuropsychopharmacol 25:817–827

Ballard ME, Mandelkern MA, Monterosso JR, Hsu E, Robertson CL, Ishibashi K, Dean AC, London ED (2015) Low dopamine D2/D3 receptor availability is associated with steep discounting of delayed rewards in methamphetamine dependence. Int J Neuropsychopharmacol 18(7):pyu119

Belujon P, Grace AA (2017) Dopamine system dysregulation in major depressive disorders. Int J Neuropsychopharmacol 20:1036–1046

Berry AS, Shah VD, Jagust WJ (2018) The influence of dopamine on cognitive flexibility is mediated by functional connectivity in young but not older adults. J Cogn Neurosci 30:1330–1344

Bickel W, Yi R (2008) Temporal discounting as a measure of executive function. In: Houser D, McCabe K (eds) Neuroeconomics, Advances in health economics and health services research, vol 20. Emerald Group, Bingley, pp 289–309

Bickel WK, Athamneh LN, Basso JC, Mellis AM, DeHart WB, Craft WH, Pope D (2019) Excessive discounting of delayed reinforcers as a trans-disease process: update on the state of the science. Curr Opin Psychol 30:59–64

Bizot JC, Chenault N, Houzé B, Herpin A, David S, Pothion S, Trovero F (2007) Methylphenidate reduces impulsive behaviour in juvenile Wistar rats, but not in adult Wistar, SHR and WKY rats. Psychopharmacology 193:215–223

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH (2010) Dopaminergic network differences in human impulsivity. Science 329(5991):532

Cardinal RN, Robbins TW, Everitt BJ (2000) The effects of d-amphetamine, chlordiazepoxide, alpha-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. Psychopharmacology 152:362–375

Chamberlain SR, Sahakian BJ (2007) The neuropsychiatry of impulsivity. Curr Opin Psychiatry 20:255–261

Chen W, Nong Z, Li Y, Huang J, Chen C, Huang L (2017) Role of dopamine signaling in drug addiction. Curr Top Med Chem 17:2440–2455

Cilia R, van Eimeren T (2011) Impulse control disorders in Parkinson's disease: seeking a roadmap toward a better understanding. Brain Struct Funct 216:289–299

Cilia R, Ko JH, Cho SS, van Eimeren T, Marotta G, Pellecchia G, Pezzoli G, Antonini A, Strafella AP (2010) Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. Neurobiol Dis 39:98–104

Cools R, Robbins TW (2004) Chemistry of the adaptive mind. Philos Trans A Math Phys Eng Sci 362:2871–2888

Cools R, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M (2008) Working memory capacity predicts dopamine synthesis capacity in the human striatum. J Neurosci 28:1208–1212

Cortés A, Moreno E, Rodríguez-Ruiz M, Canela EI, Casadó V (2016) Targeting the dopamine D3 receptor: an overview of drug design strategies. Expert Opin Drug Discovery 11:641–664

Cox SM, Frank MJ, Larcher K, Fellows LK, Clark CA, Leyton M, Dagher A (2015) Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. NeuroImage 109:95–101

Crunelle CL, Schulz S, de Bruin K, Miller ML, van den Brink W, Booij J (2011) Dose-dependent and sustained effects of varenicline on dopamine D2/3 receptor availability in rats. Eur Neuropsychopharmacol 21:205–210

Crunelle CL, de Wit TC, de Bruin K, Ramakers RM, van der Have F, Beekman FJ, van den Brink W, Booij J (2012) Varenicline increases in vivo striatal dopamine D2/3 receptor binding: an ultra-high-resolution pinhole [^{123}I]IBZM SPECT study in rats. Nucl Med Biol 39:640–644

Dajani DR, Uddin LQ (2015) Demystifying cognitive flexibility: implications for clinical and developmental neuroscience. Trends Neurosci 38:571–578

de Wit H (2009) Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addict Biol 14:22–31

de Wit H, Enggasser JL, Richards JB (2002) Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. Neuropsychopharmacology 27:813–825

Dean AC, Sevak RJ, Monterosso JR, Hellemann G, Sugar CA, London ED (2011) Acute modafinil effects on attention and inhibitory control in methamphetamine-dependent humans. J Stud Alcohol Drugs 72:943–953

Dennison O, Gao J, Lim LW, Stagg CJ, Aquili L (2019) Catecholaminergic modulation of indices of cognitive flexibility: a pharmaco-tDCS study. Brain Stimul 12:290–295

Dickman SJ (1990) Functional and dysfunctional impulsivity: personality and cognitive correlates. J Pers Soc Psychol 58:95–102

Eagle DM, Robbins TW (2003) Lesions of the medial prefrontal cortex or nucleus accumbens core do not impair inhibitory control in rats performing a stop-signal reaction time task. Behav Brain Res 146:131–144

Eagle DM, Wong JC, Allan ME, Mar AC, Theobald DE, Robbins TW (2011) Contrasting roles for dopamine D1 and D2 receptor subtypes in the dorsomedial striatum but not the nucleus accumbens core during behavioral inhibition in the stop-signal task in rats. J Neurosci 31:7349–7356

Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146:348–361

Eysenck HJ, Eysenck SBG (1975) Manual of the Eysenck Personality Questionnaire. Hodder and Stoughton, London

Fenollar-Cortés J, Gallego-Martínez A, Fuentes LJ (2017) The role of inattention and hyperactivity/impulsivity in the fine motor coordination in children with ADHD. Res Dev Disabil 69:77–84

Floresco SB, Tse MTL, Ghods-Sharifi S (2008) Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. Neuropsychopharmacology 33:1966–1979

Frost R, McNaughton N (2017) The neural basis of delay discounting: a review and preliminary model. Neurosci Biobehav Rev 79:48–65

Ghahremani DG, Tabibnia G, Monterosso J, Hellemann G, Poldrack RA, London ED (2011) Effect of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. Neuropsychopharmacology 36:950–959

Ghahremani DG, Lee B, Robertson CL, Tabibnia G, Morgan AT, De Shetler N, Brown AK, Monterosso J, Aron AR, Mandelkern MA, Poldrack RA, London ED (2012) Striatal dopamine D2/D3 receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. J Neurosci 32:7316–7324

Glahn DC, Knowles EE, Pearlson GD (2016) Genetics of cognitive control: Implications for NIMH's research domain criteria initiative. Am J Med Genet B Neuropsychiatr Genet 171B:111–120

Gray JC, Sanchez-Roige S, de Wit H, MacKillop J, Palmer AA (2019) Genomic basis of delayed reward discounting. Behav Process 162:157–161

Grillner S, Robertson B (2016) The basal ganglia over 500 million years. Curr Biol 26:R1088–R1100

Groman SM, Smith NJ, Petrullli JR, Massi B, Chen L, Ropchan J, Huang Y, Lee D, Morris ED, Taylor JR (2016) Dopamine D3 receptor availability is associated with inflexible decision making. J Neurosci 36:6732–6741

Hammes J, Theis H, Giehl K, Hoenig MC, Greuel A, Tittgemeyer M, Timmermann L, Fink GR, Drzezga A, Eggers C, van Eimeren T (2019) Dopamine metabolism of the nucleus accumbens and fronto-striatal connectivity modulate impulse control. Brain 142:733–743

Horst NK, Jupp B, Roberts AC, Robbins TW (2019) D2 receptors and cognitive flexibility in marmosets: tri-phasic dose-response effects of intra-striatal quinpirole on serial reversal performance. Neuropsychopharmacology 44:564–571

Ireland JL, Archer J (2008) Impulsivity among adult prisoners: a confirmatory factor analysis study of the Barratt Impulsivity Scale. Personal Individ Differ 45:286–292

Izquierdo A, Jentsch JD (2012) Reversal learning as a measure of impulsive and compulsive behavior in addictions. Psychopharmacology 219:607–620

Keeler JF, Pretsell DO, Robbins TW (2014) Functional implications of dopamine D1 vs. D2 receptors: a "prepare and select" model of the striatal direct vs. indirect pathways. Neuroscience 282C:156–175

Kohno M, Nurmi EL, Laughlin CP, Morales AM, Gail EH, Hellemann GS, London ED (2016a) Functional genetic variation in dopamine signaling moderates prefrontal cortical activity during risky decision-making. Neuropsychopharmacology 41:695–703

Kohno M, Okita K, Morales AM, Robertson CL, Dean AC, Ghahremani DG, Saab FW, Rawson RA, Mandelkern MA, Bilder RM, London ED (2016b) Midbrain functional connectivity and ventral-striatal dopamine D2-type receptors: link to impulsivity in methamphetamine users. Mol Psychiatry 21:1554–1560

Koob GF, Volkow ND (2010) Neurocircuitry of addiction. Neuropsychopharmacology 35:217–238
Lee B, Groman S, London ED, Jentsch JD (2007) Dopamine D2/D3 receptors play a specific role in the reversal of a learned visual discrimination in monkeys. Neuropsychopharmacology 32:2125–2134
Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, Mumford JA, Bokarius AV, Dahlbom M, Mukherjee J, Bilder RM, Brody AL, Mandelkern MA (2009) Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. J Neurosci 29(47):14734–14740
Liang CS, Ho PS, Yen CH, Chen CY, Kuo SC, Huang CC, Yeh YW, Ma KH, Huang SY (2017) The relationship between the striatal dopamine transporter and novelty seeking and cognitive flexibility in opioid dependence. Prog Neuro-Psychopharmacol Biol Psychiatry 74:36–42
Linden J, James AS, McDaniel C, Jentsch JD (2018) Dopamine D2 receptors in dopaminergic neurons modulate performance in a reversal learning task in mice. eNeuro 5. https://doi.org/10.1523/ENEURO.0229-17.2018
Logan GD (1994) On the ability to inhibit thought and action: a user's guide to the stop signal paradigm. In: Dagenbach D, Carr TH (eds) Inhibitory processes in attention, memory and language. Academic Press, San Diego
London ED, Kohno M, Morales AM, Ballard ME (2015) Chronic methamphetamine abuse and corticostriatal deficits revealed by neuroimaging. Brain Res 1628(Pt A):174–185
McDonald CE, Rossell SL, Phillipou A (2019) The comorbidity of eating disorders in bipolar disorder and associated clinical correlates characterised by emotion dysregulation and impulsivity: a systematic review. J Affect Disord 259:228–243
Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC (2001) Psychiatric aspects of impulsivity. Am J Psychiatry 158:1783–1793
Mostofsky SH, Simmonds DJ (2008) Response inhibition and response selection: two sides of the same coin. J Cogn Neurosci 20:751–761
Okita K, Morales AM, Dean AC, Johnson MC, Lu V, Farahi J, Mandelkern MA, London ED (2018) Striatal dopamine D1-type receptor availability: no difference from control but association with cortical thickness in methamphetamine users. Mol Psychiatry 23:1320–1132
Ouzir M, Errami M (2016) Etiological theories of addiction: a comprehensive update on neurobiological, genetic and behavioural vulnerability. Pharmacol Biochem Behav 148:59–68
Paterson NE, Vocci FJ, Sevak RJ, Wagreich E, London ED (2014) Dopamine D3 receptors as a therapeutic target for methamphetamine dependence. Am J Drug Alcohol Abuse 40:1–9
Patros CH, Alderson RM, Kasper LJ, Tarle SJ, Lea SE, Hudec KL (2016) Choice-impulsivity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): a meta-analytic review. Clin Psychol Rev 43:162–174
Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol 51:768–774
Perez GA, Haney M, Foltin RW, Hart CL (2008) Modafinil decreases food intake in humans subjected to simulated shift work. Pharmacol Biochem Behav 90:717–722
Petzold J, Kienast A, Lee Y, Pooseh S, London ED, Goschke T, Smolka MN (2019a) Baseline impulsivity may moderate L-DOPA effects on value-based decision-making. Sci Rep 9:5652
Petzold J, Lee Y, Pooseh S, Oehme L, Beuthien-Baumann B, London ED, Goschke T, Smolka MN (2019b) Presynaptic dopamine function measured with [^{18}F]fluorodopa and L-DOPA effects on impulsive choice. Sci Rep 9:17927
Pine A, Shiner T, Seymour B, Dolan RJ (2010) Dopamine, time, and impulsivity in humans. J Neurosci 30:8888–8896
Reise SP, Moore TM, Sabb FW, Brown AK, London ED (2013) The Barratt Impulsiveness Scale-11: reassessment of its structure in a community sample. Psychol Assess 25:631–642
Richards JB, Sabol KE, de Wit H (1999) Effects of methamphetamine on the adjusting amount procedure, a model of impulsive behavior in rats. Psychopharmacology 146:432–439
Robertson CL, Ishibashi K, Chudzynski J, Mooney LJ, Rawson RA, Dolezal BA, Cooper CB, Brown AK, Mandelkern MA, London ED (2015a) Effect of exercise training on striatal dopamine D2/D3 receptors in methamphetamine users during behavioral treatment. Neuropsychopharmacology 41:1629–1636

Robertson CL, Ishibashi K, Mandelkern MA, Brown AK, Ghahremani DG, Sabb F, Bilder R, Cannon T, Borg J, London ED (2015b) Striatal D1- and D2-type dopamine receptors are linked to motor response inhibition in human subjects. J Neurosci 35:5990–5997

Samanez-Larkin GR, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Arrington CM, Baldwin RM, Smith CE, Treadway MT, Kessler RM, Zald DH (2013) A thalamocorticostriatal dopamine network for psychostimulant-enhanced human cognitive flexibility. Biol Psychiatry 74(2):99–105

Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, Rodriguez-Sanchez JM, Rios-Lago M, Tirapu J, Barcelo F (2009) Construct validity of the trail making test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J Int Neuropsychol Soc 15:438–450

Smith KM, Xie SX, Weintraub D (2016) Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. J Neurol Neurosurg Psychiatry 87:864–870

Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH (2009) Fifty years of the Barratt Impulsiveness Scale: an update and review. Personal Individ Differ 47:385–395

Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, Taylor E, Casey BJ, Castellanos FX, Wadhwa PD (2007) Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. Neuropsychol Rev 17:39–59

Verdejo-García A, Lawrence AJ, Clark L (2008) Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. Neurosci Biobehav Rev 32:777–810

Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F (2009) Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56(Suppl 1):3–8

Volkow ND, Wise RA, Baler R (2017) The dopamine motive system: Implications for drug and food addiction. Nat Rev Neurosci 18:741–752

Voon V, Mehta AR, Hallett M (2011) Impulse control disorders in Parkinson's disease: recent advances. Curr Opin Neurol 24:324–330

Voon V, Rizos A, Chakravartty R, Mulholland N, Robinson S, Howell NA, Harrison N, Vivian G, Ray CK (2014) Impulse control disorders in Parkinson's disease: decreased striatal dopamine transporter levels. J Neurol Neurosurg Psychiatry 85:148–152

Wade TR, de Wit H, Richards JB (2000) Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. Psychopharmacology 150:90–101

Warren N, O'Gorman C, Lehn A, Siskind D (2017) Dopamine dysregulation syndrome in Parkinson's disease: a systematic review of published cases. J Neurol Neurosurg Psychiatry 88:1060–1064

Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A (2012) Question-naire for impulsive-compulsive disorders in Parkinson's Disease–Rating Scale. Mov Disord 27:242–247

Zorick T, Lee B, Mandelkern MA, Robertson C, Ghahremani DG, Brown AK, Sumerel B, London ED (2011) Low striatal dopamine receptor availability linked to caloric intake during abstinence from chronic methamphetamine abuse. Mol Psychiatry 17:569–571

Sex Differences in Neural Correlates of Inhibitory Control

Jessica Weafer

Contents

Abstract This chapter reviews the current evidence for sex differences in neural function underlying inhibitory control. Specifically, the chapter focuses on sex differences in functional magnetic resonance imaging (fMRI) measures of brain engagement during response inhibition on stop signal and go/no-go tasks. Sex differences appear to exist in these measures, but the direction of effect depends on the population studied, the task used, and whether successful or unsuccessful inhibition is examined. For successful inhibition, healthy men typically show greater brain engagement in right frontal regions typically implicated in inhibitory control (e.g., inferior frontal gyrus and supplementary motor area) than women, especially when performing the stop signal task. However, in younger populations or when

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controlling for the effects of age, women tend to show greater brain engagement than men, especially when performing the go/no-go task. For unsuccessful inhibition, women tend to show greater brain engagement compared to men in the anterior cingulate cortex and thalamus. Taken together, findings suggest that sex differences in neural responses to response inhibition depend on the specific type of inhibition studied and on whether the inhibition is successful or unsuccessful. Men exhibit greater response during successful inhibition, whereas women consistently display greater neural responses during unsuccessful inhibition. The chapter highlights limitations and gaps in this research to date, including a lack of consideration of the role of sex hormones and menstrual cycle phase, and suggests future directions for this line of research.

Keywords fMRI · Go/no-go task · Inhibitory control · Sex differences · Stop signal task

1 Introduction

Impulsivity, broadly speaking, refers to a tendency to act without foresight and without consideration of future negative consequences. Men are generally considered to be more impulsive than women and are more likely to engage in impulsive behaviors, including reckless driving, verbal and physical aggression, violent crimes, and drug use (Cross et al. 2010). In line with this, men also score higher on self-report measures of impulsivity (Cross et al. 2010). Given these sex differences in the phenomenon of impulsivity, it is important to consider sex differences in the specific components of this construct. Inhibitory control, or the ability to refrain from engaging in inappropriate or maladaptive behavior, is one important facet of impulsivity that is critical to daily life function. Individuals regularly face situations that require inhibitory control, from the decision of whether to have a second helping of dessert to the offer of a last round of drinks while out with friends. Failure to inhibit such behavior can result in undesirable consequences (e.g., weight gain, missing work due to a hangover) and difficulty maintaining optimal function. Inhibitory control (or deficits therein) is also a hallmark feature of several DSM-5 disorders, including substance use disorders (Lee et al. 2019), certain eating disorders (Wu et al. 2013), and attention-deficit/hyperactivity disorder (ADHD) (Crosbie et al. 2008). These disorders are characterized by marked difficulty in controlling behavior, and targeting inhibitory deficits is a common method of treatment (Baumeister et al. 2018; Brady et al. 2011; Manasse et al. 2020; Sofuoglu et al. 2013). As such, there has been a good deal of interest in understanding the behavioral and neural underpinnings of inhibitory control, in part to better understand risk for these disorders and to help develop more successful prevention and treatment efforts.

There is also a burgeoning interest in understanding sex differences in inhibitory control and inhibitory-related disorders. We previously reviewed the evidence for sex differences in behavioral measures of inhibitory control and found that the evidence is mixed, with results varying based on the task used to assess inhibition and the population studied (Weafer and de Wit 2014). Specifically, among healthy adults, women tend to display poorer inhibitory control on the stop signal task, whereas men tend to display poorer inhibitory control on go/no-go tasks. Finally, among individuals with substance use disorders, women show poorer inhibitory control, regardless of the task administered. Regarding the prevalence of disorders characterized by inhibitory deficits, men and women differ for several of the abovementioned disorders. For instance, males show higher rates of drug and alcohol use disorders (Grant et al. 2017; Slade et al. 2016), although this sex gap is shrinking rapidly (Keyes et al. 2011), and ADHD is more common among males than females (Polanczyk et al. 2007). On the other hand, eating disorders, including binge eating disorder and bulimia nervosa, are more common in women (Coffino et al. 2019).

This chapter reviews the current evidence for sex differences in neural correlates of inhibitory control. Identifying sex differences in brain function underlying inhibition has important implications for understanding biologically based risk for inhibitory-related disorders in men and women, as well as for developing biologically-based treatment (e.g., pharmacotherapy or noninvasive brain stimulation techniques) for these disorders. The chapter focuses on functional magnetic resonance imaging (fMRI) measures of brain engagement during successful and unsuccessful response inhibition. The chapter will describe measures commonly used to assess neural correlates of inhibitory control and give a brief overview of the neural circuitry underlying inhibition. Next, sex differences in neural function among healthy adults are discussed, including the influence of age. Given that sex differences in behavioral measures of inhibition differ for stop signal and go/no-go tasks, we review the evidence on sex differences in neural function separately for these two tasks, where appropriate. This is followed by a review of sex differences in vulnerable individuals, including those who are at risk for substance use disorders and those who have experienced early life trauma. Finally, limitations of current research are discussed and suggestions are made for future research.

2 Inhibitory Control Measures in fMRI Research

Traditional behavioral tasks used to assess inhibitory control, including the stop signal task and go/no-go task, have been adapted for use during fMRI. For stop signal tasks, participants are required to respond as quickly as possible to "go" signals (e.g., left or right pointing arrows) and to inhibit responses on a fraction of trials in which a "stop" signal (e.g., vertical arrow) is presented. On stop signal trials, the stop signal is presented soon after the go signal, and the delay between presentation of the go and stop signal varies based on the participant's performance. If a

participant successfully inhibits the response, the stop signal delay increases on the next trial (making inhibition more difficult), and if the participant fails to inhibit, the stop signal delay will decrease on the next trial (making inhibition easier). This trial-by-trial adjustment targets a 50% inhibition rate, so that all participants have approximately equal number of successful and unsuccessful inhibitions. The behavioral measure of inhibitory control on this task is the stop signal reaction time (SSRT) or the time required for an individual to inhibit a response. For go/no-go tasks, each trial presents either a "go" signal or a "no-go" signal. The behavioral measure of inhibition on this task is the number of inhibitory errors to no-go signals. An important distinction between the two tasks is that stop signal tasks require participants to stop an already-initiated response, whereas go/no-go tasks require participants to inhibit the initiation of a response. Thus, inhibition as assessed by the stop signal task can be thought of as mapping on to an individual's ability to stop oneself from engaging in an ongoing behavior, whereas inhibition as assessed by the go/no-go task can be thought of as mapping on to the ability to refrain from engaging in a behavior in the first place.

Neural correlates of inhibitory control are typically assessed either as the activation within specific brain regions or as degree of connectivity between brain regions observed during successful inhibition and during unsuccessful inhibition of a response. Brain engagement during successful inhibition is considered to provide a neural index of response inhibition, whereas brain engagement during unsuccessful inhibition is considered to provide a neural index of error processing. Error processing is important to response inhibition, as it determines how an individual updates behavior and performance to enhance likelihood of inhibition on successive trials. Together, the behavioral and neural measures on these tasks provide important information regarding individual differences in inhibitory control. As such, these tasks are well-suited for assessing sex differences in neural inhibitory function.

3 Neural Circuitry of Response Inhibition

Studies using the tasks described above during fMRI have consistently shown that frontal, striatal, and parietal regions are involved in successful inhibition. Specifically, the brain areas most strongly engaged during response inhibition include the inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), and insula (Aron et al. 2004; Bari and Robbins 2013). These regions form an inhibitory network circuitry in conjunction with the thalamus and basal ganglia that allows for the detection of stop signals and subsequent inhibition of motor responses (Boehler et al. 2010; Duann et al. 2009; Ghahremani et al. 2012). Importantly, better inhibitory control – as indicated by shorter SSRT – is associated with greater activity within these stopping-related regions (i.e., the pre-SMA, right IFG, basal ganglia, and thalamus) and less activity within default mode regions (i.e., the medial prefrontal cortex, parietal cortex, and precuneus/posterior cingulate cortex) (Congdon et al. 2010). As

Table 1 Sex differences in neural correlates of inhibitory control: successful inhibition

Sample (M:F)	Task	Analysis	Results	Regions	Reference
Healthy adults (20:20)	Stop signal	Regional activation	M > F	ACC, R MFG, R globus pallidus, R parahippocampal gyrus, R insula, medial frontal gyrus, dorsal cingulate, PCC, L SFG, L pulvinar, R putamen	Li et al. (2006)
Healthy adults (30:30)	Stop signal	Regional activation	M > F	L cerebellum, ACC, L OFG, L/R SFG, R pre-SMA, R superior colliculus	Li et al. (2009)
Healthy adults (26:45)	Go/no-go	Regional activation	F > M	R DLPFC, R VLPFC, R putamen, L MFG, L precentral gyrus; R/L inferior parietal lobule; L precuneus; R superior, middle, and inferior temporal gyri; R thalamus; L lentiform; L cerebellum	Garavan et al. (2006)
Healthy adults (13:15)	Go/no-go	Regional activation	M > F	ACC	Liu et al. (2012)
			F > M	L middle temporal gyrus	
Healthy adolescents and adults (41:25)	Stop signal	Regional activation	M > F	ACC, rostromedial frontal cortex, SMA, R inferior parietal lobule, PCC, precuneus, cuneus	Rubia et al. (2013)
			F > M	L VLPFC, L IFG, L insula, L putamen, L superior temporal cortex	
Healthy adolescents and adults (66:64)	Go/no-go	ICA	F > M	R IFG, R thalamus, isthmus cingulate cortex	Chung et al. (2020)
FHP and FHN adults (24:35)	Go/no-go	Regional activation	M > F (FHP and FHN)	L insula/IFG	Devito et al. (2013)

F female, *M* male, *L* left, *R* right, *ACC* anterior cingulate cortex, *MFG* middle frontal gyrus, *PCC* posterior cingulate cortex, *SFG* superior frontal gyrus, *OFG* orbital frontal gyrus, *SMA* supplementary motor area, *DLPFC* dorsolateral prefrontal cortex, *VLPFC* ventrolateral prefrontal cortex, *IFG* inferior frontal gyrus, *FHP* family history positive, *FHN* family history negative

for unsuccessful inhibition, the ACC is heavily involved and is thought to monitor response conflict and error processing (Hester et al. 2004; Ridderinkhof et al. 2004). The ACC works in conjunction with the insula, DLPFC, thalamus, and parietal regions to monitor errors and adjust behavior accordingly (Luijten et al. 2014).

Below we review the evidence for sex differences in neural function within this circuitry during both successful (Table 1) and unsuccessful (Table 2) inhibition. Most studies directly contrasted brain activity in men and women and reported regions in which one sex had greater brain activation relative to the other sex. This

Table 2 Sex differences in neural correlates of inhibitory control: unsuccessful inhibition

Sample (M:F)	Task	Analysis	Results	Regions	Reference
Healthy adults (30:30)	Stop signal	Regional activation	F > M	ACC, R thalamus, R superior colliculus	Li et al. (2009)
Healthy adolescents and adults (66:64)	Go/no-go	ICA	F > M	R IFG, R thalamus, isthmus cingulate cortex, L amygdala	Chung et al. (2020)
FHP and FHN adults (24:35)	Go/no-go	Regional activation	F > M (FHP adults)	R/L thalamus	Devito et al. (2013)
Social drinkers (68:77)	Stop signal	Regional activation	F > M	R/L thalamus, middle and superior temporal cortex, ACC	Ide et al. (2018)

F female, *M* male, *L* left, *R* right, *ACC* anterior cingulate cortex, *IFG* inferior frontal gyrus, *FHP* family history positive, *FHN* family history negative

chapter follows the same approach and the term "greater" is used to report regions of activity or connectivity in which one sex shows more engagement relative to the other. Sex differences in behavioral task performance are reported throughout as well. In most studies, men and women did not differ on task performance. When sex differences were observed in performance, these differences were typically controlled for in fMRI analyses.

4 Sex Differences in Neural Correlates of Inhibition in Healthy Adults

4.1 Stop Signal Task

Investigations of sex differences in neural correlates of inhibitory control on the stop signal task point toward greater brain activity in men. In an initial study, men ($N = 20$) showed greater activity than women ($N = 20$) in frontal regions, including middle and medial frontal cortices and the ACC, as well as the globus pallidus and putamen, parahippocampal gyrus, posterior cingulate cortex (PCC), and thalamus (Li et al. 2006). Women did not show greater activity than men in any regions. For a second follow-up study (Li et al. 2009), the authors added an additional 10 men and 10 women to the original sample, for a total of $N = 30$ men and $N = 30$ women. Here they examined sex differences during both successful and unsuccessful inhibition. For successful inhibition, men again showed greater activity than women in frontal regions, including the frontopolar and perigenual ACC, as well as the orbital frontal gyrus, bilateral superior frontal gyrus, and anterior pre-SMA, and the superior colliculus and cerebellum. There were no regions where women showed greater activity than men during successful response inhibition. For unsuccessful inhibition, women showed greater activity than men in the ACC, thalamus, and superior

colliculus. Finally, it is important to note that men and women did not differ in behavioral task performance in either study. In sum, while performing the stop signal task, men showed greater activity in frontal and subcortical regions than women during successful inhibition, whereas women showed greater thalamus and ACC activity than men during unsuccessful inhibition.

4.2 Go/No-Go Task

There is mixed evidence for sex differences in neural correlates of response inhibition on the go/no-go task. In a large study that combined 5 datasets for a total sample of $N = 71$ (45 women and 26 men), Garavan et al. (2006) reported greater activity in women compared to men during successful inhibition in predominately right-lateralized frontal, parietal, temporal, and subcortical regions. Specifically, women had greater activation in the right DLPFC and ventrolateral prefrontal cortex (VLPFC), right putamen, left middle frontal gyrus (MFG), and left precentral gyrus; bilateral inferior parietal lobule and left precuneus; right superior, middle, and inferior temporal gyri; and right thalamus and left lentiform and cerebellum. A second study of sex differences in go/no-go task activation examined 28 healthy volunteers (15 women and 13 men) and found greater activation during successful inhibition in women compared to men in the left middle temporal gyrus. By contrast, men showed greater activation than women in the ACC (Liu et al. 2012). As with the stop signal studies, men and women did not differ in behavioral performance of the go/no-go task in either study.

4.3 Summary

Taken together, these studies provide evidence for sex differences in neural inhibitory function among healthy adults. However, the direction of the difference is not clear and may vary depending on the task administered and whether successful or unsuccessful inhibition is examined. For successful inhibition, the two stop signal studies (which included overlapping samples) reported greater brain activity in men compared to women in frontal and subcortical regions. On the other hand, the two go/no-go studies reported mixed results. Although both studies found greater activity in women in temporal regions, Garavan et al. (2006) also reported greater activity in women in frontal and parietal regions, whereas Liu et al. (2012) reported greater activity in men in the ACC. For unsuccessful inhibition, women showed greater activation than men on the stop signal task, particularly in the ACC and thalamus. Overall, men tend to display greater brain activity during response inhibition on stop signal tasks, when inhibiting an already-initiated response. By contrast, women tend to display greater brain activity during inhibition on go/no-go tasks, when inhibiting

the initiation of a response. Women also show greater activity during response inhibition errors.

5 Influence of Age on Sex Differences in Neural Correlates of Inhibition in Healthy Adults

Inhibitory control over behavior increases throughout adolescence and into early adulthood (Bedard et al. 2002; Williams et al. 1999; Fosco et al. 2019; Crosbie et al. 2013). Correspondingly, functional activation within lateral and medial fronto-striatal inhibitory circuits also increases throughout this period, even after controlling for performance differences across age groups (for a review, see Rubia et al. 2013). As such, it is important to consider age-related factors that contribute to sex differences in neural inhibitory function. The studies reviewed below examine potential sex differences in the development of neural correlates of inhibitory control from childhood to adulthood.

5.1 Stop Signal Task

One study to date has examined the influence of age on sex differences in neural inhibitory function on the stop signal task. The authors analyzed sex differences in brain activity during successful inhibition in healthy adolescents and adults ($N = 66$; 41 males and 25 females) ranging in age from 13 to 45 years (Rubia et al. 2013). In terms of behavioral performance, females had a shorter SSRT than males, indicating better inhibitory control. After controlling for sex differences in task performance, females displayed greater activity than males in the left ventrolateral, superior, and inferior frontal cortices, superior temporal lobe, insula, and putamen. Activity in three of these regions (i.e., left VLPFC, left superior prefrontal cortex, and left putamen) was correlated with age, such that activity in these regions increased with age specifically in females. Males had greater activity than females in rostromedial frontal cortex, including the ACC and SMA, as well as the right inferior parietal lobe and PCC/precuneus. Two of these regions (i.e., right inferior parietal/postcentral gyrus and left superior frontal lobe) exhibited responses that were correlated with age, such that activity in these regions increased with age only in males. The authors concluded that sex differences in neural inhibitory function, specifically right-lateralized activity in males and left-lateralized activity in females, are due to sex differences in maturation of neural circuitry.

5.2 Go/No-Go Task

A second study examined the influence of age on sex differences in functional connectivity during response inhibition on the go/no-go task (Chung et al. 2020). Participants were healthy volunteers ($N = 130$, 66 males and 64 females) ranging in age from 12 to 25 years. There were no sex differences in behavioral task performance. The authors used a high-order independent component analysis (ICA) to estimate sex differences in functional connectivity during both successful and unsuccessful inhibition. This analysis typically identifies single regions with highly correlated fMRI time courses. Results showed greater regional functional connectivity in females compared to males in the isthmus cingulate cortex, right IFG, and right thalamus during both successful and unsuccessful inhibition and the left amygdala during unsuccessful inhibition only. Results also showed a significant sex x age interaction in two components: left IFG during both successful and unsuccessful inhibition and bilateral superior parietal during successful inhibition only. For both components, females showed a negative correlation between connectivity strength and inhibition with age, whereas no associations were observed in males. Finally, the authors examined sex differences in functional network connectivity by testing pairwise correlations between components. Results showed predominately greater network connectivity in females compared to males, including between superior parietal lobule and both PCC and inferior parietal lobule, as well as between ACC and inferior parietal lobule. By contrast, males showed greater connectivity than females between precentral gyrus and inferior parietal lobule. The authors concluded that the observed sex differences indicate that functional inhibitory networks operate differently in females and males during adolescence.

5.3 Summary

Together, these studies provide preliminary information on sex differences in maturation of neural inhibitory function over development and how such differences in development influence sex differences in neural inhibitory function in adulthood. In both studies, females displayed greater engagement within neural inhibitory circuitry, as well as stronger correlations between engagement (particularly the left IFG) and age. However, the direction of the association between brain engagement and age in females differed across studies. Specifically, age was positively correlated with IFG activity on the stop signal task, whereas age was negatively correlated with IFG regional functional connectivity during the go/no-go task. Taken together, these two studies suggest that males and females differ in patterns of maturation of neural circuitry related to inhibitory control, with females showing more pronounced changes in brain engagement during development than males. These developmental differences likely influence sex differences in neural inhibitory function in adulthood.

6 Sex Differences in Neural Correlates of Inhibition in Vulnerable Individuals

As stated above, poor inhibitory control is linked to several DSM-5 disorders, including substance use disorder, eating disorders, and ADHD. The sections below review evidence to date for sex differences in neural inhibitory function in individuals at risk for these types of disorders.

6.1 Individuals at Risk for Substance Use Disorders

Poor inhibitory control is strongly implicated in substance use disorders, as both a cause and consequence of problematic substance use. Individuals with substance use disorders perform more poorly on behavioral measures of inhibitory control (Weafer et al. 2014; Perry and Carroll 2008), and they also display less brain activity during response inhibition (Luijten et al. 2014). Importantly, men and women with substance use disorders differ in behavioral measures of inhibitory control, with heavy drinking women showing poorer inhibitory control than heavy drinking men (Weafer and de Wit 2014; Townshend and Duka 2005; Nederkoorn et al. 2009). This suggests that substance users may show similar sex differences in neural correlates of inhibitory control. The sections below review findings from investigations of sex differences in neural inhibitory function among individuals with, or at risk for, substance use disorders.

Alcohol Several studies have examined sex differences in neural inhibitory function in individuals who currently have, or are at risk for developing, alcohol use disorder (AUD). For example, Ide et al. (2018) assessed sex differences in brain engagement during stop signal task performance in male ($N = 68$) and female ($N = 77$) social drinkers. Men and women did not differ in behavioral task performance. Sex differences in brain activity during successful inhibition were not reported. For unsuccessful inhibition, women showed greater activity than men in the thalamus, middle and superior temporal gyrus, and dorsal ACC. Further, less error-related activity in the thalamus was associated with higher Alcohol Use Disorders Identification Test (AUDIT) scores in women, but not in men. In a second study, Devito et al. (2013) assessed sex differences in brain engagement during the go/no-go task in individuals who were at risk for AUD as indicated by family history of alcoholism. Participants were healthy, non-substance abusing men ($N = 24$) and women ($N = 35$) who were either family history positive (FHP) or family history negative (FHN). Again, there were no sex differences in behavioral performance. For successful inhibition, a trend-level sex difference was observed, with greater activity in the left insula/IFG in men compared to women. For unsuccessful inhibition, sex differences were dependent on family history status. Specifically, among FHP individuals only, women had greater activity than men in bilateral thalamus. No

sex differences were observed in FHN individuals. Taken together, these findings suggest that sex differences in error processing in the thalamus (i.e., greater thalamic activity in women compared to men) may influence sex differences in vulnerability for problematic alcohol use.

Cocaine One study to date has examined sex differences in neural inhibitory function in relation to cocaine use. This study, which utilized a stop signal task, did not directly examine sex differences in neural inhibitory function but instead tested sex differences in neural predictors of relapse in cocaine-dependent individuals (Luo et al. 2013). There were no sex differences in behavioral performance. Analyses of fMRI data focused on unsuccessful inhibition. For women ($N = 37$), less activity in the bilateral thalamus and dorsal ACC during unsuccessful inhibition predicted relapse to cocaine use. For men ($N = 60$), less activity in the left insula and dorsal ACC predicted relapse. These relationships were observed even after controlling for history of cocaine and alcohol use.

Summary Sex differences in neural inhibitory function among substance users and those at risk for substance use disorder have been primarily observed during unsuccessful inhibition (i.e., error processing). Specifically, among substance users, women tend to show greater thalamic and ACC activity during inhibitory errors than men. Further, among women only, there is a negative relationship between thalamic activity during unsuccessful inhibition and substance use. Specifically, greater thalamic error-related activity in women is associated with lesser severity of alcohol consumption and alcohol-related problems among drinkers (Ide et al. 2018) and relapse among cocaine-dependent individuals (Luo et al. 2013). As such, thalamic error-related activity may be protective for females in general, such that the greater thalamic activity observed in women compared to men may contribute to the lesser prevalence of substance use disorders in women overall. However, for the subset of women who have low thalamic activity, this may be an important sex-specific risk factor for substance use. Finally, these findings suggest that, as with behavioral studies, neural inhibitory function may be more strongly related to risk for substance use in women than in men.

6.2 Individuals Who Experienced Early Life Stress

Early life stressors are associated with poor behavioral and neural measures of inhibitory control (Farah et al. 2006; Mueller et al. 2010). Additionally, the negative effects of early life stress tend to be more pronounced in females compared to males (Holbrook et al. 2002), suggesting that there may be sex differences in the impact of early life stress on inhibitory control specifically. The studies below investigated potential sex differences in the influence of such stressors, including childhood maltreatment and low socioeconomic status (SES), on brain engagement during inhibition.

Childhood Maltreatment Sex differences have been reported in the degree to which childhood maltreatment predicts neural correlates of inhibition. In a retrospective design, adults ($N = 21$ women and $N = 19$ men) reported on childhood maltreatment using the Childhood Trauma Questionnaire (CTQ) and performed the stop signal task during fMRI (Elton et al. 2014). The authors used ICA to identify an inhibitory control network that was active during successful inhibition. They then tested associations between childhood maltreatment and network activation and connectivity. There were no sex differences in behavioral performance. There was, however, an interaction between sex, CTQ, and SSRT on the strength of functional connectivity. Specifically, for females, stronger network functional connectivity was associated with shorter SSRT (better inhibition) for those with low CTQ scores and longer SSRT (poorer inhibition) for those with high CTQ scores. The opposite direction of effects was observed for males. Further analyses showed that connectivity of the inferior frontal cortex and dorsal ACC significantly accounted for sex differences in effects of childhood maltreatment on overall network connectivity.

Low SES Sex differences have also been reported in the degree to which low SES influences development of neural inhibitory function over adolescence. In a longitudinal design, Spielberg et al. (2015) examined the influence of SES and age on sex differences in neural correlates of inhibition on the go/no-go task. Healthy adolescents ($N = 63$; 28 females and 35 males) performed the task once at the onset of adolescence (mean age = 11 for girls and 12 for boys, due to earlier onset of puberty in girls) and then again 2 years later (mean age = 13 for girls and 14 for boys). For the behavioral data, there was an interaction between sex and SES on change in inhibitory performance over time. Among girls, lower SES was associated with decreased inhibitory accuracy over time, whereas SES was not associated with change in inhibitory performance in boys. Imaging data were analyzed in a block design, such that brain engagement during inhibition was averaged across successful and unsuccessful inhibitions. As with the behavioral data, there was also an interaction between sex and SES in the imaging data. For girls, lower SES was associated with greater ACC activation during inhibition over time, but no significant relationships were observed in boys. This finding held after controlling for age. Further, greater ACC activation was correlated with poorer inhibition accuracy over time in girls. Finally, connectivity analyses showed that for low SES girls only, connectivity between the ACC and both DLPFC and IFG decreased over time. In sum, low SES was associated with poorer behavioral inhibition, greater ACC activity, and less ACC to right frontal connectivity over time in early adolescence in girls, but not boys.

Summary Taken together, these studies show that there are sex-specific effects of childhood adversity on neural inhibitory function. Both studies highlighted the ACC as a region that is sensitive to childhood adversity, especially in females. Moreover, both studies found that ACC–IFG/DLPFC connectivity was particularly relevant to sex differences in effects of childhood adversity.

7 General Summary

Overall, the studies reviewed here suggest that there are important sex differences in neural correlates of inhibitory control. However, these differences vary depending on the population studied, the task used, and whether successful or unsuccessful inhibition is examined. Among healthy adults, most studies point toward greater brain activity in men during successful inhibition, especially when performing the stop signal task. However, when studying younger populations and incorporating the effects of age, females tend to show greater brain activity during successful inhibition, especially when performing the go/no-go task. Among individuals with, or at risk for, substance use disorders, women tend to show greater brain activity during inhibitory errors than compared to men. Finally, women tend to be more sensitive than men to the effects of childhood adversity on neural inhibitory function.

7.1 Limitations and Future Directions

There are several important gaps in the literature to date on sex differences in neural inhibitory function. First, none of the studies reviewed above included measures of sex hormones or menstrual cycle phase in women. This is an important omission, as there is evidence from both behavioral and neuroimaging studies that inhibitory function in women varies across the menstrual cycle. For example, Colzato et al. (2010) reported an association between estradiol level and behavioral performance on the stop signal task, such that higher estradiol was associated with poorer inhibition. Further, women displayed poorer inhibitory control in the late follicular phase, when estradiol is high, compared to the early follicular or mid-luteal phase. In line with this, sex differences were observed in the late follicular phase (with women displaying poorer inhibitory control than men), but no sex differences were observed during the early follicular or mid-luteal phases. Additionally, there is initial neuroimaging evidence that activity and connectivity of the basal ganglia during response inhibition differ across the menstrual cycle (Hidalgo-Lopez and Pletzer 2019). However, no studies to date have incorporated sex hormones into analyses of sex differences in neural inhibitory function. It will be important for future studies to assess the influence of sex hormones and menstrual cycle phase on sex differences in brain activity during inhibition to more fully understand the biological factors influencing sex differences in inhibitory control.

Second, the degree to which sex differences in neural activity relate to sex differences in behavior is not well-understood. The majority of studies reviewed here reported sex differences in neural function, but no sex differences in inhibitory control task performance. As such, it is difficult to interpret the functional impact of sex differences in the brain on behavior. One interpretation is that fMRI measures are more sensitive measures of sex differences than behavioral task performance (Luijten et al. 2014), and sex differences might be expected on task performance

if, for example, the sample size were increased. This interpretation is in line with our conclusions from a previous review of studies that investigated sex differences in behavioral measures of inhibitory control (Weafer and de Wit 2014). The behavioral studies in our previous review typically consisted of larger samples sizes than the fMRI studies reviewed here. In behavioral studies, men tend to display greater inhibitory control on stop signal tasks and women tend to show greater inhibitory control on go/no-go tasks. Likewise, in fMRI studies, men tend to show greater brain activity on stop signal tasks and women tend to display greater brain activity on go/no-go tasks. Another interpretation is that more brain activity indicates that more neural resources are required to perform at a comparable level (Li et al. 2006). This interpretation would suggest that men have poorer inhibitory control on stop signal tasks and women have poorer inhibitory control on go/no-go tasks. It will be important for future studies to explicitly assess associations between neural and behavioral correlates of inhibitory control in women and men to help clarify the functional significance of observed sex differences.

Third, there is still little information on sex differences in neural inhibitory function among individuals with disorders characterized by poor inhibitory control. As reviewed above, initial studies have examined sex differences among individuals with or at risk for substance use disorder. However, to our knowledge, no studies to date have examined sex differences in brain engagement during response inhibition in individuals with ADHD or eating disorders. Moreover, the studies examining individuals with substance use disorder have been cross-sectional for the most part. More longitudinal studies are needed to assess whether observed sex differences in neural correlates of inhibition are a cause or consequence of substance use and other inhibitory disorders. This information will help develop sex-specific intervention methods targeting neural inhibitory function in the prevention and treatment of these disorders.

In sum, we are just beginning to understand how men and women differ in neural inhibitory function. The mixed findings to date are likely due to a number of factors that contribute to difficulties in replicating imaging findings, including small sample sizes, variability in analytic approach, and variability in motion correction methodology. It is likely that some of the apparent discrepancies across studies may resolve themselves as more studies are completed. It will be important for future studies to determine how sex differences in neural function translate to sex differences in behavior and, importantly, sex differences in disorders characterized by poor inhibitory control. This understanding has the potential to have important implications for sex-specific prevention and treatment efforts for substance use disorders and other inhibitory-related functions.

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References

Aron AR, Robbins TW, Poldrack RA (2004) Inhibition and the right inferior frontal cortex. Trends Cogn Sci 8(4):170–177

Bari A, Robbins TW (2013) Inhibition and impulsivity: behavioral and neural basis of response control. Prog Neurobiol 108:44–79

Baumeister S, Wolf I, Holz N, Boecker-Schlier R, Adamo N, Holtmann M, Ruf M, Banaschewski T, Hohmann S, Brandeis D (2018) Neurofeedback training effects on inhibitory brain activation in ADHD: a matter of learning? Neuroscience 378:89–99

Bedard AC, Nichols S, Barbosa JA, Schachar R, Logan GD, Tannock R (2002) The development of selective inhibitory control across the life span. Dev Neuropsychol 21(1):93–111

Boehler CN, Appelbaum LG, Krebs RM, Hopf JM, Woldorff MG (2010) Pinning down response inhibition in the brain—conjunction analyses of the stop-signal task. NeuroImage 52 (4):1621–1632

Brady KT, Gray KM, Tolliver BK (2011) Cognitive enhancers in the treatment of substance use disorders: clinical evidence. Pharmacol Biochem Behav 99(2):285–294

Chung YS, Calhoun V, Stevens MC (2020) Adolescent sex differences in cortico-subcortical functional connectivity during response inhibition. Cogn Affect Behav Neurosci 20(1):1–18

Coffino JA, Udo T, Grilo CM (2019) Rates of help-seeking in US adults with lifetime DSM-5 eating disorders: prevalence across diagnoses and differences by sex and ethnicity/race. In: Mayo Clinic proceedings, vol 94(8). Elsevier, Amsterdam, pp 1415–1426

Colzato LS, Hertsig G, van den Wildenberg WP, Hommel B (2010) Estrogen modulates inhibitory control in healthy human females: evidence from the stop-signal paradigm. Neuroscience 167 (3):709–715

Congdon E, Mumford JA, Cohen JR, Galvan A, Aron AR, Xue G et al (2010) Engagement of large-scale networks is related to individual differences in inhibitory control. NeuroImage 53 (2):653–663

Crosbie J, Perusse D, Barr CL, Schachar RJ (2008) Validating psychiatric endophenotypes: inhibitory control and attention deficit hyperactivity disorder. Neurosci Biobehav Rev 32 (1):40–55

Crosbie J, Arnold P, Paterson A, Swanson J, Dupuis A, Li X et al (2013) Response inhibition and ADHD traits: correlates and heritability in a community sample. J Abnorm Child Psychol 41 (3):497–507

Cross CP, Copping LT, Campbell A (2010) Sex differences in impulsivity: a meta-analysis. Psychol Bull 137(1):97–130

DeVito EE, Meda SA, Jiantonio R, Potenza MN, Krystal JH, Pearlson GD (2013) Neural correlates of impulsivity in healthy males and females with family histories of alcoholism. Neuropsychopharmacology 38(10):1854–1863

Duann JR, Ide JS, Luo X, Li CSR (2009) Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 29 (32):10171–10179

Elton A, Tripathi SP, Mletzko T, Young J, Cisler JM, James GA, Kilts CD (2014) Childhood maltreatment is associated with a sex-dependent functional reorganization of a brain inhibitory control network. Hum Brain Mapp 35(4):1654–1667

Farah MJ, Shera DM, Savage JH, Betancourt L, Giannetta JM, Brodsky NL et al (2006) Childhood poverty: specific associations with neurocognitive development. Brain Res 1110(1):166–174

Fosco WD, Hawk LW Jr, Colder CR, Meisel SN, Lengua LJ (2019) The development of inhibitory control in adolescence and prospective relations with delinquency. J Adolesc 76:37–47

Garavan H, Hester R, Murphy K, Fassbender C, Kelly C (2006) Individual differences in the functional neuroanatomy of inhibitory control. Brain Res 1105(1):130–142

Ghahremani DG, Lee B, Robertson CL, Tabibnia G, Morgan AT, De Shetler N et al (2012) Striatal dopamine D2/D3 receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. J Neurosci 32(21):7316–7324

Grant BF, Chou SP, Saha TD, Pickering RP, Kerridge BT, Ruan WJ et al (2017) Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on alcohol and related conditions. JAMA Psychiat 74(9):911–923

Hester R, Fassbender C, Garavan H (2004) Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the GO/NOGO task. Cereb Cortex 14 (9):986–994

Hidalgo-Lopez E, Pletzer B (2019) Individual differences in the effect of menstrual cycle on basal ganglia inhibitory control. Sci Rep 9(1):1–11

Holbrook TL, Hoyt DB, Stein MB, Sieber WJ (2002) Gender differences in long-term posttraumatic stress disorder outcomes after major trauma: women are at higher risk of adverse outcomes than men. J Trauma Acute Care Surg 53(5):882–888

Ide JS, Zhornitsky S, Chao HH, Zhang S, Hu S, Wang W et al (2018) Thalamic cortical error–related responses in adult social drinkers: sex differences and problem alcohol use. Biol Psychiatry Cogn Neurosci Neuroimaging 3(10):868–877

Keyes KM, Li G, Hasin DS (2011) Birth cohort effects and gender differences in alcohol epidemiology: a review and synthesis. Alcohol Clin Exp Res 35(12):2101–2112

Lee RSC, Hoppenbrouwers S, Franken I (2019) A systematic meta-review of impulsivity and compulsivity in addictive behaviors. Neuropsychol Rev 29(1):14–26

Li CSR, Huang C, Constable RT, Sinha R (2006) Gender differences in the neural correlates of response inhibition during a stop signal task. NeuroImage 32(4):1918–1929

Li CSR, Zhang S, Duann JR, Yan P, Sinha R, Mazure CM (2009) Gender differences in cognitive control: an extended investigation of the stop signal task. Brain Imaging Behav 3(3):262–276

Liu J, Zubieta JK, Heitzeg M (2012) Sex differences in anterior cingulate cortex activation during impulse inhibition and behavioral correlates. Psychiatry Res Neuroimaging 201(1):54–62

Luijten M, Machielsen MW, Veltman DJ, Hester R, de Haan L, Franken IH (2014) Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. J Psychiatry Neurosci 39(3):149–169

Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM et al (2013) Error processing and gender-shared and-specific neural predictors of relapse in cocaine dependence. Brain 136(4):1231–1244

Manasse SM, Lampe EW, Gillikin L, Payne-Reichert A, Zhang F, Juarascio AS, Forman EM (2020) The project REBOOT protocol: evaluating a personalized inhibitory control training as an adjunct to cognitive behavioral therapy for bulimia nervosa and binge-eating disorder. Int J Eat Disord

Mueller SC, Maheu FS, Dozier M, Peloso E, Mandell D, Leibenluft E et al (2010) Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. Neuropsychologia 48(10):3037–3044

Nederkoorn C, Baltus M, Guerrieri R, Wiers RW (2009) Heavy drinking is associated with deficient response inhibition in women but not in men. Pharmacol Biochem Behav 93(3):331–336

Perry JL, Carroll ME (2008) The role of impulsive behavior in drug abuse. Psychopharmacology 200(1):1–26

Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatr 164(6):942–948

Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. Science 306(5695):443–447

Rubia K, Lim L, Ecker C, Halari R, Giampietro V, Simmons A et al (2013) Effects of age and gender on neural networks of motor response inhibition: from adolescence to mid-adulthood. NeuroImage 83:690–703

Slade T, Chapman C, Swift W, Keyes K, Tonks Z, Teesson M (2016) Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: systematic review and metaregression. BMJ Open 6(10):e011827

Sofuoglu M, DeVito EE, Waters AJ, Carroll KM (2013) Cognitive enhancement as a treatment for drug addictions. Neuropharmacology 64:452–463

Spielberg JM, Galarce EM, Ladouceur CD, McMakin DL, Olino TM, Forbes EE et al (2015) Adolescent development of inhibition as a function of SES and gender: converging evidence from behavior and fMRI. Hum Brain Mapp 36(8):3194–3203

Townshend JM, Duka T (2005) Binge drinking, cognitive performance and mood in a population of young social drinkers. Alcohol Clin Exp Res 29(3):317–325

Weafer J, de Wit H (2014) Sex differences in impulsive action and impulsive choice. Addict Behav 39(11):1573–1579

Weafer J, Mitchell SH, de Wit H (2014) Recent translational findings on impulsivity in relation to drug abuse. Curr Addict Rep 1(4):289–300

Williams BR, Ponesse JS, Schachar RJ, Logan GD, Tannock R (1999) Development of inhibitory control across the life span. Dev Psychol 35(1):205–213

Wu M, Hartmann M, Skunde M, Herzog W, Friederich HC (2013) Inhibitory control in bulimic-type eating disorders: a systematic review and meta-analysis. PLoS One 8(12):e83412

Part II
Behavioral Processes

The Genetics of Externalizing Problems

Peter B. Barr and Danielle M. Dick

Contents

Abstract Externalizing problems generally refer to a constellation of behaviors and/or disorders characterized by impulsive action and behavioral disinhibition. Phenotypes on the externalizing spectrum include psychiatric disorders, nonclinical behaviors, and personality characteristics (e.g. alcohol use disorders, other illicit substance use, antisocial behaviors, risky sex, sensation seeking, among others). Research using genetic designs including latent designs from twin and family data and more recent designs using genome-wide data reveal that these behaviors and problems are genetically influenced and largely share a common genetic etiology.

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Large-scale gene-identification efforts have started to identify robust associations between genetic variants and these phenotypes. However, there is still considerable work to be done. This chapter provides an overview of the current state of research into the genetics of behaviors and disorders on the externalizing spectrum.

Keywords Externalizing · Genetics · GWAS · Polygenic scores

1 Introduction

Externalizing problems refer to a constellation of behaviors and/or disorders characterized by impulsive action and/or behavioral undercontrol. Externalizing problems can be contrasted with internalizing problems in that they typically reflect actions in the external world, rather than internalized processes within the self, such as anxiety, depression, or negative affect. Externalizing problems include a variety of behaviors such as alcohol or substance misuse, antisocial behaviors, aggression, and risk taking (Krueger et al. 2002; Salvatore and Dick 2018; Young et al. 2000).

Problems associated with externalizing behaviors have high social costs. Substance misuse remains one of the leading contributors to preventable mortality and morbidity worldwide. In 2016, alcohol use contributed 4.2% of the total global burden of disease; other drug use contributed to 1.3% of the total global disease burden; and smoking contributed to approximately 12% of all deaths (Degenhardt et al. 2013; Reitsma et al. 2017). In 2017, over 47,000 Americans died as the result of an opioid overdose (Center for Disease Control and Prevention 2019). In addition to the health consequences, these behaviors have significant financial costs. Each year, excessive alcohol use is estimated to cost the United States $250 billion (Sacks et al. 2015). Illicit drugs cost the United States approximately $190 billion (National Drug Intelligence Center 2011) annually, of which $78.5 billion is due to opioid use alone (Florence et al. 2016). And while difficult to calculate, the total cost of crime in the United States is estimated between $690 billion to $3.41 trillion annually (Maurer 2017). Understanding the etiology of these behaviors is of utmost importance for practitioners and policy makers to effectively design prevention and intervention efforts.

2 Epidemiology of Externalizing Behaviors/Disorders

Behaviors and disorders across the externalizing spectrum are highly prevalent. The 12-month prevalence for substance use disorders (SUD) in the United States is approximately 14% for alcohol use disorders (AUD) and 4% for other substance use disorders (SUD), while the lifetime prevalence is much higher (~29% for AUD and ~10% for SUD) (Grant et al. 2015, 2016). These disorders typically manifest during young adulthood, with mean ages of onset ranging from 23.9 for SUD to 26.2

for AUD (Grant et al. 2015, 2016). The lifetime prevalence for other psychiatric disorders related to impulse control, such as attention hyperactivity deficit disorder (ADHD) and conduct disorder (CD), are 5.1% and 9.5%, respectively, and these appear at earlier ages (7 and 13 years old, respectively) (Kessler et al. 2005a; Polanczyk et al. 2007). Taken together, the prevalence for *any* disorder related to impulse control is high: 24.8%, with a median age of onset = 11 years old (Kessler et al. 2005a). Importantly, substance use and impulse control disorders do not manifest in isolation and show strong comorbidity in past 12-month diagnoses (Grant et al. 2015, 2016; Kessler et al. 2005b). Longitudinal analyses reveal that many externalizing problems, including heavy alcohol use (Chen and Jacobson 2012), illicit drug use (Chen and Jacobson 2012), and antisocial behaviors (Powell et al. 2010), increase across adolescence into young adulthood, followed by a steady decline. Overall, behaviors on the externalizing spectrum are common, with significant variation across the life course.

2.1 Genetic Epidemiology of the Externalizing Spectrum

Twin and family designs use information from close relatives to estimate the heritability[1] of a trait. Twin studies allow researchers to decompose the variance in a trait into additive genetic, shared environmental, and unique environmental influences by comparing the phenotypic correlations of monozygotic (MZ) and dizygotic (DZ) twin pairs. We can estimate these variances due to the fact that MZ twins share all of their genetic variation, while DZ twins share half of their genetic variation, on average. Shared environmental influences, which refer to environments that make twins more similar, include conditions such as neighborhood context, family socioeconomic status, and religion. Unique environmental influences refer to experiences that have the effect of making twins more different from each other than expected based on their genetic sharing, for example, if one twin experiences a trauma, or has a different peer group. When the within-pair MZ correlation for a phenotype is larger than the within-pair DZ correlation, this suggests the importance of genetic influences on the trait under study. When the DZ correlation for a phenotype is more than half of the MZ correlation, this suggests the presence of shared environmental influences. When the MZ correlation is less than unity, unique environmental influences are inferred (measurement error is also confounded with unique environmental influences) (Neale and Cardon 2013).

Many of the individual phenotypes on the externalizing spectrum demonstrate modest to considerable heritability (h^2). SUD have moderate genetic influences, with

[1]Heritability (h^2) generally refers to broad sense heritability, or the proportion of variance in a population that is the result of genetic influences. Twin and family models generally divide variance in a phenotype into additive genetic (A), shared environmental (C), and unique environmental (E) variance. Unique environmental influences also include measurement error.

~50% of the variance in AUD (Verhulst et al. 2015), 50–60% of the variance in problematic cannabis use (Verweij et al. 2010), ~40–80% of the variance in cocaine use disorders (Kendler et al. 2000, 2003a), 20–50% of the variation in opioid dependence (Kendler et al. 2003a; van den Bree et al. 1998), and ~60% of the variance in nicotine dependence (Maes et al. 2004) being due to genetic influences (h^2). Related psychiatric and behavioral outcomes, such as ADHD ($h^2 = 74\%$), antisocial behavior ($h^2 = 32\%$), rule breaking ($h^2 = 48\%$), and aggression ($h^2 = 65\%$), are moderately-to-strongly heritable (Burt 2009; Faraone and Larsson 2019; Rhee and Waldman 2002).

Importantly, while the heritability for each of these individual phenotypes is moderate-to-strong, the genetic variation impacting each of these disorders appears to be largely shared. Each of these phenotypes load onto a single highly heritable (h^2 ~80%) externalizing factor (Kendler et al. 2003b; Krueger et al. 2002; Young et al. 2000), which explains a large proportion of the genetic variance in each individual trait. For example, a general externalizing factor explains 74–80% of genetic influences for AUD, 62–74% for other SUD, and 57–92% for antisocial personality disorder (Kendler and Myers 2013). Other nonclinical risky behaviors that load on to this genetic factor for externalizing include driving while drunk, earlier age at first sex, and riskier sex (Harden et al. 2008b; Quinn and Harden 2013; Samek et al. 2014). Finally, in addition to behaviors, personality traits of novelty seeking, sensation seeking, lack of agreeableness, and lack of conscientiousness also load strongly on this externalizing factor (Kendler and Myers 2013; Krueger et al. 2002; Mann et al. 2015; Young et al. 2000). Overall, twin and family studies indicate that common genetic influences impact multiple traits on the externalizing spectrum.

2.2 *Changes in the Etiology of Externalizing Problems Across Development*

Like many other complex traits, genetic influences on externalizing problems change across the life course. Genetic influences generally become more important as individuals age and begin to achieve more independence (Dick 2011a; Kendler et al. 2008; Long et al. 2017). This is especially true for traits on the externalizing spectrum. Twin studies repeatedly show that shared environment has important effects on substance use/misuse in early life, whereas genetic influences become more important as individuals reach early adulthood (Dick 2011a; Kendler et al. 2008; Long et al. 2017). Figure 1 provides an overview of the changing relative influence of genetic and shared environmental variance over adolescence (Dick 2011a).

While the *importance* of genetic influences appears to increase over the early life course, there is evidence that the *source* of genetic influences is relatively stable over time. Multivariate twin models find that the majority of genetic influence on externalizing is attributable to a single factor that explains a large portion of the variance

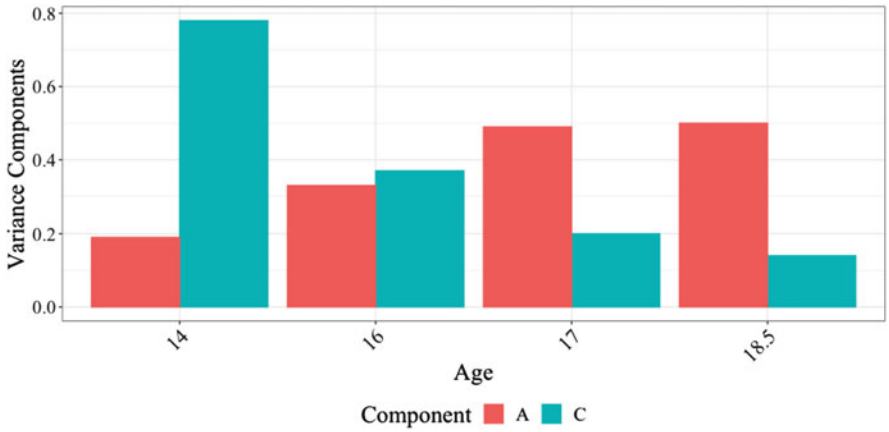

Fig. 1 Relative importance of additive genetic (A) and shared environmental (C) influences on alcohol initiation and frequency of use across adolescence (data reported in Dick 2011a). Across adolescence additive genetic influences (A) become more important, while shared environmental influences (C) become less important

across development (Wichers et al. 2013). Longitudinal models demonstrate that the genetic influences on initial levels of externalizing mostly overlap with the genetic influences on change over time (Hatoum et al. 2018). In other words, the genetic influences that influence externalizing problems in early development also affect behaviors during adolescence. These patterns are similar when we look at specific behaviors on the externalizing spectrum, including alcohol use (Long et al. 2017) and problematic alcohol use (van Beek et al. 2012): the sources of genetic influences are fairly stable across time. Stability in the source of genetic influences over development also occurs with the personality correlates of externalizing problems (Briley and Tucker-Drob 2017). Longitudinal analyses of lab-based tasks related to both impulsivity and delay discounting reveal developmentally stable, genetic influences on these measures meant to assess dimensions of personality (Anokhin et al. 2011; Niv et al. 2012). Overall, it appears that while genetic influences may become more important over time, the same genetic influences act across development.

Despite the evidence that genetic influences on externalizing are stable over development, there is some evidence that the specificity of genetic influences can change for certain phenotypes on the externalizing spectrum. This is especially apparent in regards to alcohol misuse. Genetic risk for broader externalizing problems and genetic risk for AUD both independently predict alcohol misuse across early development. However, the effect size for each form of genetic risk changes over time. In adolescence, broader externalizing risk has a stronger effect on alcohol misuse, while alcohol specific risk becomes important during adulthood (see Fig. 2) (Kendler et al. 2011; Meyers et al. 2014). For other drug use, common genetic influences explain approximately half of the correlation between externalizing problems in childhood and drug initiation in late adolescence (Korhonen et al. 2012).

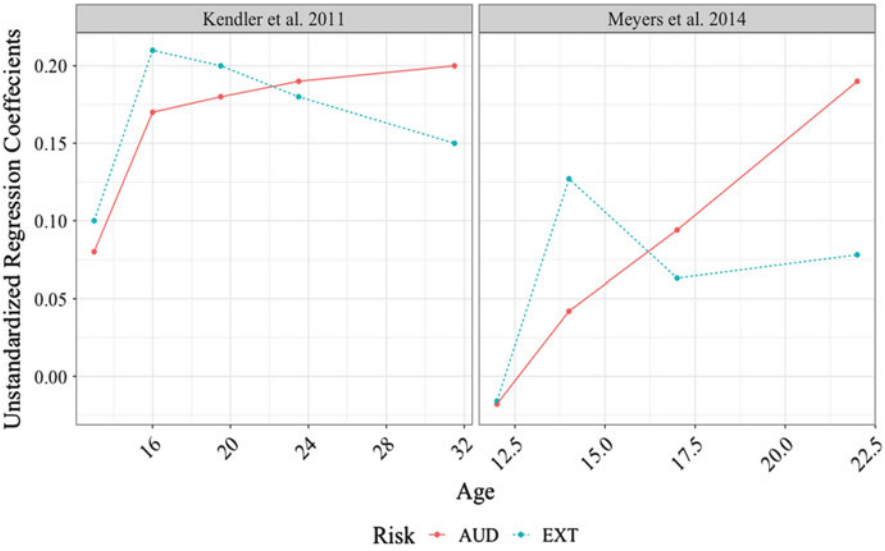

Fig. 2 Genetic risk and alcohol phenotypes from Kendler et al. (2011) and Meyers et al. (2014). Regression coefficients between genetic risk specific to AUD (AUD) or broader externalizing disorders (EXT) and alcohol consumption across age in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPUD, left) and the Finnish Twin Cohort (FinnTwin12, right). Genetic risk for broader externalizing problems and genetic risk specific to AUD both independently predict alcohol misuse across development, though the effect sizes for each changes over time. In adolescence, EXT has a stronger effect on alcohol misuse, while AUD becomes important during adulthood

2.3 Gene-Environment Interactions in Externalizing Problems

Environmental conditions can alter the importance of genetic influences on externalizing behaviors. This phenomenon is referred to as gene-environment interaction, or GxE (Dick 2011b). Researchers have put forth a variety of theoretical models of GxE. For externalizing phenotypes, we see consistent evidence for two primary theoretical paradigms of GxE: the social control/opportunity model and the social distinction model (Boardman et al. 2013; Shanahan and Hofer 2005). Under the social control/opportunity model of GxE, genetic influences become more important under conditions of reduced social control or increased social opportunity (Shanahan and Hofer 2005). For example, environmental conditions related to low social control/increased social opportunity, such as peer deviance (Cooke et al. 2015; Harden et al. 2008a; Mann et al. 2016; Samek et al. 2016) or high neighborhood turnover rate (Dick et al. 2009), are associated with increases in genetic influences on various externalizing traits. On the opposite side, environmental conditions associated with greater social control/reduced social opportunity, such as greater parental monitoring (Cooke et al. 2015; Dick et al. 2007) or involvement in a committed

relationship (Barr et al. 2017; Heath et al. 1989), are associated with reduced genetic influences on these phenotypes. It is important to note that this model of GxE spans various externalizing phenotypes including alcohol use, smoking, behavior problems, and delinquency (Cooke et al. 2015; Harden et al. 2008a; Mann et al. 2016; Samek et al. 2016).

Under the social distinction model of GxE (Boardman et al. 2013), certain social conditions "push" the phenotype and increase the importance of environmental influences on a trait at one end of the environmental spectrum. This increase in the importance of environmental variance reduces the importance of genetic influences on that same end of the spectrum. For externalizing problems, childhood socioeconomic status (SES) has consistently fit this model of GxE. Childhood SES moderates the effect of genetic variation on externalizing problems, such that under conditions of lower SES, environmental sources of variance are more important than genetic influences (Middeldorp et al. 2014; Tuvblad et al. 2006). Family SES moderates genetic liability for externalizing whereby higher SES and higher genetic risk are associated with a steeper increase in alcohol problems across adolescence (Barr et al. 2018). Neighborhood-level SES, moderates genetic risk on delinquency (Beaver 2011) and non-violent conduct problems (Burt et al. 2016) in the same direction as family-level SES, such that environmental influences are stronger under conditions of low neighborhood SES. Overall, GxE findings for the social distinction model and social control/opportunity model demonstrate the ways in which the importance genetic influences can shift across environmental conditions.

3 Molecular Genetic Studies of Externalizing Problems

While twin and family data provide valuable insight into the genetics of externalizing problems and other complex traits, they use a latent approach that does not provide information about the specific genetic variants associated with a given trait. Over the past 20 years, the growth in research examining measured genetic variants has rapidly expanded. Much of the early work focused on candidate genes, which were proposed to be associated with a trait because of a hypothesized biological mechanism. Research in this tradition largely focused on genes or single nucleotide polymorphisms (SNPs) in the serotonergic or dopaminergic region. However, candidate gene research has been plagued by false positives, publication bias, and low powered studies (Duncan and Keller 2011). Recent large-scale meta-analyses reveal no support for much of the early work on candidate gene analyses (Border et al. 2019), suggesting that our "best guesses" for genes involved in the underlying biology were not very good. Importantly, candidate gene studies do not fit with our current polygenic understanding of complex traits, whereby phenotypes are influenced by many variants (in the hundreds, if not thousands) of very small effect (Visscher et al. 2017).

With the mapping of the human genome, the focus on candidate gene research has given way to agnostic methods of gene identification that scan the entire genome for

SNPs associated with a given trait. Rather than focusing on a single variant with some hypothesized biological mechanism, genome-wide association studies, or GWAS, test the association between a phenotype and SNPs spanning the entire genome. Because of the large number of tests (the typical *p*-value for genome-wide significance, or GWS, is $p < 5 \times 10^{-8}$ to correct for approximately one million independent tests) and small effect sizes associated with individual variants, adequate sample sizes for discovery GWAS likely require hundreds of thousands to millions of individuals. Fortunately, with the growth of cheaply available genotyping arrays, large-scale biobanks that genotype large numbers of individuals, and direct-to-consumer genetic testing companies that amass genotypic information on large samples, the sample sizes for these GWAS have been rapidly increasing (Mills and Rahal 2019).

3.1 Current GWAS of Externalizing Phenotypes

Table 1 provides a sampling of the current GWAS for externalizing traits. To date, these GWAS have predominantly focused on single phenotypes that would be considered part of the externalizing spectrum, mostly substance use outcomes. The majority of GWAS on substance use have focused on alcohol-related phenotypes, including alcohol dependence (Walters et al. 2018) (3 GWS SNPs), alcohol use disorder (Kranzler et al. 2019) (10 GWS SNPs), number of alcoholic drinks per week (Liu et al. 2019) (156 GWS SNPs), and maximum alcohol intake (Gelernter et al. 2019) (6 GWS SNPs). A SNP in the *ADH1B* gene region (rs1229984) responsible for alcohol metabolism is the most consistently associated SNP across these alcohol GWAS (Gelernter et al. 2019; Kranzler et al. 2019; Liu et al. 2019; Walters et al. 2018); however, other genome-wide significant variants have also begun to emerge, such as those in *GCKR* which is involved in sugar metabolism in the liver and pancreas (Gelernter et al. 2019; Kranzler et al. 2019; Liu et al. 2019). Sample sizes for these alcohol phenotypes have ranged from moderately to extremely well powered (*N*'s ~50k – one million). Interestingly, these GWAS reveal that genetic influences on alcohol consumption only partially overlap with variants that impact alcohol-related problems (Sanchez-Roige et al. 2018; Walters et al. 2018).

GWAS of some illicit drugs, especially cannabis phenotypes, are beginning to reach sample sizes that have adequate power for detection of genetic effects. A recent GWAS of lifetime cannabis use (Pasman et al. 2018) (*N* ~180K) identified eight GWS SNPs. Three of these loci were in the *CADM2*, which has also shown up in GWAS of impulsivity (Sanchez-Roige et al. 2019), alcohol consumption (Clarke et al. 2017), number of offspring (Day et al. 2016), and risk-taking behavior (Day et al. 2016; Karlsson Linnér et al. 2019). A GWAS of cannabis use disorder (Demontis et al. 2019a) in ~50K individuals identified a single GWS SNP that is a strong expression quantitative trait locus (eQTL, a variant that influences the expression of a gene or genes) for *CHRNA2*, a nicotine receptor gene related to smoking behavior (Liu et al. 2019). GWAS of other illicit substance use disorders, including

Table 1 Current GWAS of externalizing phenotypes

Phenotype	Domain	*N*	Publication
Alcohol dependence[a]	Substance use	52,848	Walters et al. (2018)
Alcohol use disorders[a]	Substance use	274,424	Kranzler et al. (2019)
Alcohol consumption	Substance use	941,280	Liu et al. (2019)
Maximum alcohol intake[a]	Substance use	143,965	Gelernter et al. (2019)
Cannabis use disorder	Substance use	51,372	Demontis et al. (2019a, b)
Lifetime Cannabis use	Substance use	184,765	Pasman et al. (2018)
Ever smoker	Substance use	1,232,091	Liu et al. (2019)
Drug experimentation	Substance use	22,861	Sanchez-Roige et al. (2019)
Broad antisocial behavior	Risky/problem behaviors	16,400	Tielbeek et al. (2017)
Risky behaviors	Risky/problem behaviors	315,894	Karlsson Linnér et al. (2019)
Number of sexual partners	Risky/problem behaviors	370,711	Karlsson Linnér et al. (2019)
ADHD	Other psychiatric disorders	53,293	Demontis et al. (2019a, b)
Barratt impulsiveness scale	Personality characteristics	22,861	Sanchez-Roige et al. (2019)
UPPS-P impulsive behavior scale	Personality characteristics	22,861	Sanchez-Roige et al. (2019)
Delay discounting	Personality characteristics	23,217	Sanchez-Roige et al. (2019)
General risk tolerance	Personality characteristics	939,908	Karlsson Linnér et al. (2019)

[a]Multi-ancestry sample

cocaine dependence (Gelernter et al. 2014) and opioid dependence (Cheng et al. 2018), are currently underpowered due to extremely small sample sizes (*N* ~2,500–7,500). Overall, larger sample sizes are needed across illicit substance use to better detect variants associated with these phenotypes.

Beyond substance use, GWAS have focused on other disorders and personality traits related to the externalizing spectrum. A recent GWAS of ADHD (Demontis et al. 2019b) (*N* ~55K) identified 12 GWS loci. Several of the loci associated with ADHD are located in or near genes implicated in neurodevelopmental processes, including *FOXP2*, *SORCS3*, and *DUSP6* (Demontis et al. 2019b). For other behavioral phenotypes, a GWAS of antisocial behaviors in ~16k individuals using a broad variety of behaviors (including conduct disorder, behavior check lists, and other scales of antisocial behaviors) did not identify any genome-wide significant loci. GWAS of impulsivity scales including the Barratt Impulsiveness Scale, or BIS (Sanchez-Roige et al. 2019), the composite UPPS-P scale (urgency, premeditation, perseverance, sensation seeking, and positive urgency), and its subscales identified GWAS SNPs in the *CADM2* gene region for the sensation seeking subscale of the UPPS-P and *CACNA1I* (which encodes for a protein thought to be involved in

calcium signaling in neurons) gene region for the negative urgency subscale (Sanchez-Roige et al. 2019).

Recently, a GWAS of general risk tolerance in approximately 940K individuals identified 124 independent GWS loci (Karlsson Linnér et al. 2019). This study also examined a composite index of risky behaviors (defined as the first principal component of ever smoking, drinks per week, automobile speeding, and number of sexual partners, $N = 315{,}894$) identifying 106 GWS SNPs. The top variants in this GWAS were in the *MAPT*, *CADM2*, and *FOXP1* gene regions, again implicating genes thought to be involved in neurodevelopmental processes (Karlsson Linnér et al. 2019).

Overall, current gene identification efforts for externalizing traits have begun to detect robust associations with individual disorders/phenotypes on the externalizing spectrum, and more recently, with general externalizing behavior. However, much remains to be discovered as to the biological mechanisms through which these variants influence behavior. While some variants have well-known biological function (such as alcohol metabolism or nicotine receptor genes), others (such as those related to neurodevelopmental processes and brain function) need further scrutiny. Future research will need to move beyond simple associations. Integrating data from human GWAS into model organisms will allow us to directly test the biological function of genes identified in GWAS and whether or not these genes exert some causal influence on externalizing problems (Baker et al. 2011; Jay 2012). As the cost of whole genome sequencing comes down, we will also be better able to examine the impact of rare variants, which are largely excluded from current methods (which focus primarily on common variants). Finally, as we begin to think of genes and variants as parts of dense networks, we may better understand the underlying biological mechanisms between genotype and phenotype (Visscher et al. 2017).

3.2 Genetic Correlations and Multivariate Genomic Methods

Perhaps the most interesting finding to emerge from all of these GWAS of phenotypes on the externalizing spectrum is the strong genetic overlap between traits, confirming earlier results from twin and family studies. Alcohol use disorder, alcohol consumption, smoking status, lifetime cannabis use, risky behaviors, general risk tolerance, and polysubstance use all have significant genetic correlations with one another (Kranzler et al. 2019; Liu et al. 2019; Meyers et al. 2014; Sanchez-Roige et al. 2019; Walters et al. 2018). These externalizing phenotypes also overlap genetically with other socio-demographic outcomes related to externalizing, including age at first birth, number of children, and educational attainment (Kranzler et al. 2019; Sanchez-Roige et al. 2019; Walters et al. 2018). Figure 3[2] shows the genetic

[2]We would like to thank Richard Karlsson-Linnér for his work gathering these GWAS summary statistics, cleaning the data, and running bivariate LDSC.

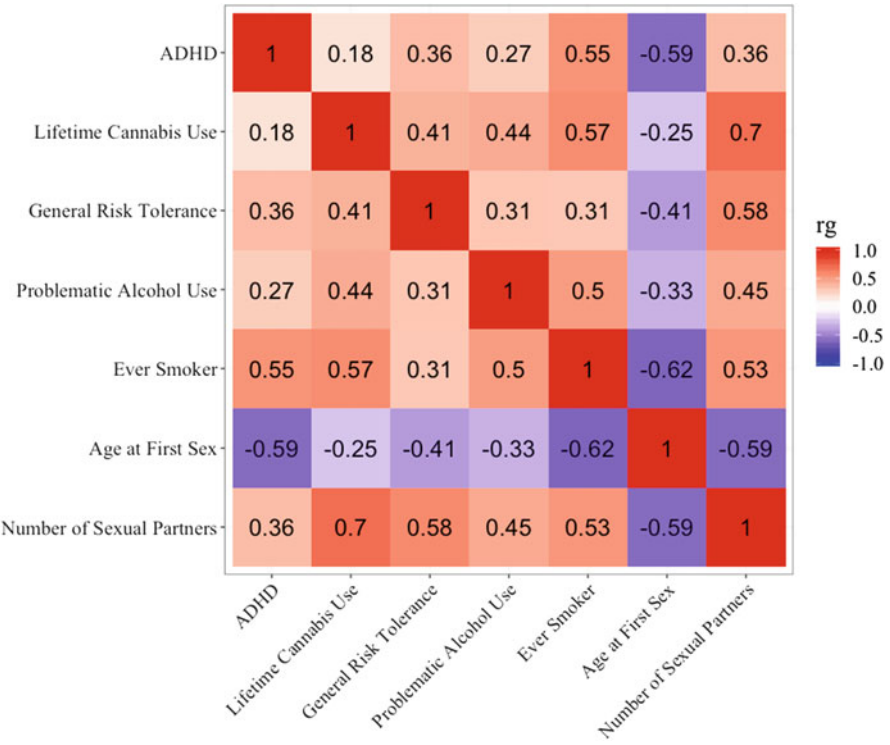

Fig. 3 Genetic correlations calculated from published GWAS of externalizing phenotypes (using bivariate LD score regression). Heatmap of genetic correlation using effect sizes from currently published GWAS, with correlation estimates denoted in the cells. There is a strong pattern of significant genetic overlap between clinically relevant phenotypes (Problematic Alcohol Use, ADHD), other substance use (Lifetime Cannabis Use, Ever Smoker), risky sexual behaviors (Age at First Sex, Number of Sexual Partners), and personality (General Risk Tolerance). The results in the heatmap demonstrate a potential shared genetic influence across these phenotypes. All genetic correlations are significant after correcting for multiple testing ($p < 0.0024$)

correlations between a subset of externalizing phenotypes, estimated using GWAS summary statistics (Demontis et al. 2019b; Karlsson Linnér et al. 2019; Liu et al. 2019; Pasman et al. 2018; Sanchez-Roige et al. 2018; Walters et al. 2018). Genetic correlations were calculated using bivariate LD score regression (Bulik-Sullivan et al. 2015).

There are now concerted efforts to use information from these and other GWAS to move beyond *univariate* analyses and model the *multivariate* genetic architecture of externalizing problems identified in twin and family studies. One such ongoing project is the Externalizing Consortium (Dick et al. 2018). New multivariate gene identification methods such as Genomic Structural Equation Modeling, or Genomic SEM (Grotzinger et al. 2019), utilize genetic correlations to model the underlying

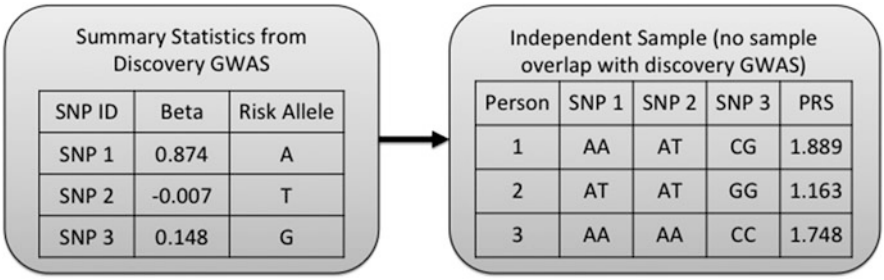

Fig. 4 Hypothetical example for calculating polygenic risk scores. Example of using GWAS summary statistics (left) to calculate polygenic risk scores (PRS) in an independent sample. GWAS provides the effect sizes (Beta) and Risk allele to calculate the weighted sum of risk alleles that an individual in the target sample carries. For example, Person 1 carries two risk alleles (A) at SNP 1, a single risk allele (T) at SNP 2, and a single risk allele (G) at SNP 3. Therefore, there PRS would be $2*0.874 + 1*-0.007 + 1*0.148 = 1.889$. This process occurs across all SNPs included for calculating a given PRS for each person in the independent target sample

factor structure of a set of phenotypes using GWAS summary statistics. While traditional SEM models the phenotypic covariance to measure a latent factor, Genomic SEM models a latent genetic factor based on the genetic covariance. Utilizing these new multivariate methods allows one to boost power to identify genetic variants by harnessing existing GWAS of genetically correlated phenotypes. This type of multivariate analysis illustrates the advantage of combining information across externalizing traits to detect genetic variants associated with a range of externalizing outcomes. As more well-powered GWAS of externalizing phenotypes become available, we will be able to model the underlying externalizing spectrum with even more power and precision.

3.3 Research Using PRS for Externalizing Phenotypes

Beyond identifying associations between individual variants and a phenotype, GWAS results can be used to create polygenic risk scores (PRS) that index an individual's overall liability for the outcomes, in order to study associations between these aggregate measures of genetic risk and phenotypes in external samples. An important component of using PRS is that the sample in which they are used must be independent of the discovery GWAS sample. Figure 4 provides an overview of how PRS are constructed. PRS are computed as the average of the number of "risk" alleles that an individual carries weighted by the parameter estimates (e.g., betas, odds ratios, and Z-scores) identified in a GWAS. Because SNPs that are close to one another in the genome correlated (referred to as linkage disequilibrium, or LD), PRS are generally constructed from a subset of independent SNPs. These SNPs can be selected using a variety of methods including "pruning and thresholding," where SNPs below a certain GWAS p-value and LD threshold (using r^2) are included

(International Schizophrenia Consortium 2009); or LDpred, which uses a Bayesian approach to model SNP effect sizes while accounting for LD from an external reference panel (Vilhjalmsson et al. 2015).

PRS provide a flexible way of taking results from large-scale GWAS into samples with extensive phenotyping or longitudinal data to answer more nuanced questions about how genetic liability unfolds over time or how it changes across the specific environments. Extending the twin-family literature, research that uses PRS for externalizing problems has also found evidence of GxE. Following the social control/social opportunity model of GxE from the twin literature, recent work using PRS has found evidence of romantic partnerships moderating the association between PRS and alcohol misuse (Barr et al. 2019); peer deviance and parental monitoring moderating the association between PRS and externalizing disorders (Salvatore et al. 2014); and neighborhood social cohesion moderating the association between PRS and nicotine use (Meyers et al. 2013). In each of the listed PRS analyses, the association between the PRS and the corresponding phenotype was stronger under conditions of reduced social control (e.g., not in a relationship, association with deviant peers, low parental monitoring, and low neighborhood social cohesion) compared to the conditions of increased control/reduced opportunity.

PRS derived from GWAS of other outcomes that are genetically correlated to externalizing problems can also be used as proxies for PRS of externalizing problems. For example, PRS derived from a GWAS of educational attainment (Lee et al. 2018) predict antisocial behaviors across the life course, from early adolescence into adulthood (Wertz et al. 2018). PRS derived from GWAS of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) also predict childhood behavior problems (Jansen et al. 2018). Finally, PRS derived from a GWAS of educational attainment predict a variety of substance use disorders, including alcohol, tobacco, and cannabis use disorders (Salvatore et al. 2019). These analyses demonstrate that in the absence of well-powered GWAS of externalizing problems, PRS derived from large GWAS of genetically correlated phenotypes provide information as to how these forms of genetic liability unfold over time and relate to multiple externalizing phenotypes.

It is important to note that even though PRS have proven to be a useful tool for understanding genetic liability, even in large cohorts, PRS continue to predict only small portions of the variance in independent samples. For example, PRS from a recent GWAS approximately one million explained ~2.5% of variance in alcohol consumption (Liu et al. 2019). Additionally, PRS aggregate information from across the genome without regards to the biological function of the variants included. Future methods that can incorporate additional information from biological annotations or functional enrichment may improve our ability to predict these disorders from PRS (Márquez-Luna et al. 2019).

3.4 Increasing Diversity in Genetic Research

Concerted efforts to increase the diversity of participants in genomic research are vital. To date, large scale GWAS are composed almost entirely of individuals of European ancestry (Mills and Rahal 2019). Inclusion of individuals of diverse ancestries is scientifically important because including diverse ancestries increases the discovery power in GWAS (Dick et al. 2017; Wojcik et al. 2019) and differences in LD structure across allow us to get closer to causal variants (Bigdeli et al. 2019). Creating more diverse samples is also important for ethical reasons. PRS derived from ancestral populations that differ from the target sample perform poorly (Martin et al. 2017). In the push towards precision medicine, the current GWAS will likely exacerbate health disparities rather than help solve them (Martin et al. 2019). Therefore, greater diversity in genomic research is both a moral and scientific imperative.

4 Conclusion

Research into the etiology of externalizing problems has found that each of the psychiatric disorders, nonclinical behaviors, and personality characteristics on the externalizing spectrum are heritable to varying degrees. Overall, these externalizing problems share a common genetic etiology that accounts for a large share of the genetic variance in each of the corresponding phenotypes. However, the importance of these genetic influences can change across developmental and environmental context, typically becoming more influential as individuals reach young adulthood and under conditions in which social control is limited. Recent work has moved beyond the latent genetic designs of twin and family research into designs using measure genome-wide data. While we have begun to robustly detect variants associated with these traits, there is still considerable work to be done on elucidating biological mechanisms of risk. Future multivariate GWAS efforts will help to better understand the underlying genetic architecture shared across individual phenotypes. As we better understand the genetic architecture, we will be able to use results to create more powerful PRS in independent samples to further explore the ways in which risk unfolds across time and environmental context. And as we move towards the era of precision medicine, we will need to ensure that we have even larger discovery samples of diverse ancestries so that our results are able to be used to improve the health of all individuals in the population.

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References

Anokhin AP, Golosheykin S, Grant JD, Heath AC (2011) Heritability of delay discounting in adolescence: a longitudinal twin study. Behav Genet 41:175–183. https://doi.org/10.1007/s10519-010-9384-7

Baker EJ, Jay JJ, Bubier JA, Langston MA, Chesler EJ (2011) GeneWeaver: a web-based system for integrative functional genomics. Nucleic Acids Res 40:D1067–D1076. https://doi.org/10.1093/nar/gkr968

Barr PB et al (2017) Social relationships moderate genetic influences on heavy drinking in Young adulthood. J Stud Alcohol Drugs 78:817–826

Barr PB, Silberg J, Dick DM, Maes HH (2018) Childhood socioeconomic status and longitudinal patterns of alcohol problems: variation across etiological pathways in genetic risk. Soc Sci Med 209:51–58. https://doi.org/10.1016/j.socscimed.2018.05.027

Barr PB et al (2019) Polygenic risk for alcohol misuse is moderated by romantic partnerships. Addiction 114:1753. https://doi.org/10.1111/add.14712

Beaver KM (2011) Environmental moderators of genetic influences on adolescent delinquent involvement and victimization. J Adolesc Res 26:84–114. https://doi.org/10.1177/0743558410384736

Bigdeli TB et al (2019) Contributions of common genetic variants to risk of schizophrenia among individuals of African and Latino ancestry. Mol Psychiatry. https://doi.org/10.1038/s41380-019-0517-y

Boardman JD, Daw J, Freese J (2013) Defining the environment in gene--environment research: lessons from social epidemiology. Am J Public Health 103:S64–S72. https://doi.org/10.2105/AJPH.2013.301355

Border R, Johnson EC, Evans LM, Smolen A, Berley N, Sullivan PF, Keller MC (2019) No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. Am J Psychiatry 176:376–387. https://doi.org/10.1176/appi.ajp.2018.18070881

Briley DA, Tucker-Drob EM (2017) Comparing the developmental genetics of cognition and personality over the life span. J Pers 85:51–64. https://doi.org/10.1111/jopy.12186

Bulik-Sullivan BK et al (2015) LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 47:291–295. https://doi.org/10.1038/ng.3211

Burt SA (2009) Are there meaningful etiological differences within antisocial behavior? Results of a meta-analysis. Clin Psychol Rev 29:163–178. https://doi.org/10.1016/j.cpr.2008.12.004

Burt SA, Klump KL, Gorman-Smith D, Neiderhiser JM (2016) Neighborhood disadvantage alters the origins of Children's nonaggressive conduct problems. Clin Psychol Sci 4:511–526. https://doi.org/10.1177/2167702615618164

Center for Disease Control and Prevention (2019) Mortality Data—National Vital Statistics System. https://www.cdc.gov/nchs/nvss/deaths.htm

Chen P, Jacobson KC (2012) Developmental trajectories of substance use from early adolescence to young adulthood: gender and racial/ethnic differences. J Adolesc Health 50:154–163. https://doi.org/10.1016/j.jadohealth.2011.05.013

Cheng Z, Zhou H, Sherva R, Farrer LA, Kranzler HR, Gelernter J (2018) Genome-wide association study identifies a regulatory variant of RGMA associated with opioid dependence in European Americans. Biol Psychiatry 84:762–770. https://doi.org/10.1016/j.biopsych.2017.12.016

Clarke TK et al (2017) Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). Mol Psychiatry 22:1376. https://doi.org/10.1038/mp.2017.153. https://www.nature.com/articles/mp2017153#supplementary-information

Cooke ME et al (2015) Gene-environment interaction effects of peer deviance, parental knowledge and stressful life events on adolescent alcohol use. Twin Res Hum Genet 18:507–517. https://doi.org/10.1017/thg.2015.56

Day FR et al (2016) Physical and neurobehavioral determinants of reproductive onset and success. Nat Genet 48:617. https://doi.org/10.1038/ng.3551. https://www.nature.com/articles/ng.3551#supplementary-information

Degenhardt L et al (2013) The global epidemiology and contribution of Cannabis use and dependence to the global burden of disease: results from the GBD 2010 study. PLoS One 8: e76635. https://doi.org/10.1371/journal.pone.0076635

Demontis D et al (2019a) Genome-wide association study implicates CHRNA2 in cannabis use disorder. Nat Neurosci 22:1066–1074. https://doi.org/10.1038/s41593-019-0416-1

Demontis D et al (2019b) Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51:63–75. https://doi.org/10.1038/s41588-018-0269-7

Dick DM (2011a) Developmental changes in genetic influences on alcohol use and dependence. Child Dev Perspect 5:223–230. https://doi.org/10.1111/j.1750-8606.2011.00207.x

Dick DM (2011b) Gene-environment interaction in psychological traits and disorders. Annu Rev Clin Psychol 7:383–409. https://doi.org/10.1146/annurev-clinpsy-032210-104518

Dick DM, Viken R, Purcell S, Kaprio J, Pulkkinen L, Rose RJ (2007) Parental monitoring moderates the importance of genetic and environmental influences on adolescent smoking. J Abnorm Psychol 116:213–218. https://doi.org/10.1037/0021-843X.116.1.213

Dick DM, Bernard M, Aliev F, Viken R, Pulkkinen L, Kaprio J, Rose RJ (2009) The role of socioregional factors in moderating genetic influences on early adolescent behavior problems and alcohol use. Alcohol Clin Exp Res 33:1739–1748. https://doi.org/10.1111/j.1530-0277.2009.01011.x

Dick DM, Barr P, Guy M, Nasim A, Scott D (2017) Review: genetic research on alcohol use outcomes in African American populations: a review of the literature, associated challenges, and implications. Am J Addict 26:486–493. https://doi.org/10.1111/ajad.12495

Dick DM et al (2018) Using the genetic architecture of externalizing disorders to aid in gene identification. Paper presented at the annual meeting of the behavior genetics association, Boston, MA

Duncan LE, Keller MC (2011) A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. Am J Psychiatry 168:1041–1049. https://doi.org/10.1176/appi.ajp.2011.11020191

Faraone SV, Larsson H (2019) Genetics of attention deficit hyperactivity disorder. Mol Psychiatry 24:562–575. https://doi.org/10.1038/s41380-018-0070-0

Florence CS, Zhou C, Luo F, Xu L (2016) The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care 54:901–906. https://doi.org/10.1097/MLR.0000000000000625

Gelernter J, Sherva R, Koesterer R, Almasy L, Zhao H, Kranzler HR, Farrer L (2014) Genome-wide association study of cocaine dependence and related traits: FAM53B identified as a risk gene. Mol Psychiatry 19:717–723. https://doi.org/10.1038/mp.2013.99

Gelernter J et al (2019) Genomewide Association Study of Maximum Habitual Alcohol Intake in >140,000 US European-and African-American Veterans Yields Novel Risk Loci Biological Psychiatry

Grant BF et al (2015) Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on alcohol and related conditions III. JAMA Psychiat 72:757–766. https://doi.org/10.1001/jamapsychiatry.2015.0584

Grant BF et al (2016) Epidemiology of DSM-5 drug use disorder: results from the National Epidemiologic Survey on alcohol and related conditions–III. JAMA Psychiat 73:39–47. https://doi.org/10.1001/jamapsychiatry.2015.2132

Grotzinger AD et al (2019) Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. Nat Hum Behav 3:513. https://doi.org/10.1038/s41562-019-0566-x

Harden KP, Hill JE, Turkheimer E, Emery RE (2008a) Gene-environment correlation and interaction in peer effects on adolescent alcohol and tobacco use. Behav Genet 38:339–347. https://doi.org/10.1007/s10519-008-9202-7

Harden KP, Mendle J, Hill JE, Turkheimer E, Emery RE (2008b) Rethinking timing of first sex and delinquency. J Youth Adolesc 37:373–385. https://doi.org/10.1007/s10964-007-9228-9

Hatoum AS, Rhee SH, Corley RP, Hewitt JK, Friedman NP (2018) Etiology of stability and growth of internalizing and externalizing behavior problems across childhood and adolescence. Behav Genet 48:298. https://doi.org/10.1007/s10519-018-9900-8

Heath AC, Jardine R, Martin NG (1989) Interactive effects of genotype and social environment on alcohol consumption in female twins. J Stud Alcohol 50:38–48

International Schizophrenia Consortium (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460:748–752. https://doi.org/10.1038/nature08185

Jansen PR et al (2018) Polygenic scores for schizophrenia and educational attainment are associated with behavioural problems in early childhood in the general population. J Child Psychol Psychiatry 59:39–47. https://doi.org/10.1111/jcpp.12759

Jay JJ (2012) Chapter one – cross species integration of functional genomics experiments. In: Chesler EJ, Haendel MA (eds) International review of neurobiology, vol 104. Academic Press, London, pp 1–24. https://doi.org/10.1016/B978-0-12-398323-7.00001-X

Karlsson Linnér R et al (2019) Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet 51:245–257. https://doi.org/10.1038/s41588-018-0309-3

Kendler KS, Myers J (2013) The boundaries of the internalizing and externalizing genetic spectra in men and women. Psychol Med 44:647–655. https://doi.org/10.1017/S0033291713000585

Kendler KS, Karkowski LM, Neale MC, Prescott CA (2000) Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. JAMA Psychiat 57:261–269. https://doi.org/10.1001/archpsyc.57.3.261

Kendler KS, Jacobson KC, Prescott CA, Neale MC (2003a) Specificity of genetic and environmental risk factors for use and abuse/dependence of Cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. Am J Psychiatry 160:687–695. https://doi.org/10.1176/appi.ajp.160.4.687

Kendler KS, Prescott CA, Myers J, Neale MC (2003b) The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry 60:929–937. https://doi.org/10.1001/archpsyc.60.9.929

Kendler KS, Schmitt E, Aggen SH, Prescott CA (2008) Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. Arch Gen Psychiatry 65:674–682. https://doi.org/10.1001/archpsyc.65.6.674

Kendler KS, Gardner C, Dick DM (2011) Predicting alcohol consumption in adolescence from alcohol-specific and general externalizing genetic risk factors, key environmental exposures and their interaction. Psychol Med 41:1507–1516. https://doi.org/10.1017/S003329171000190X

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005a) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 62:593–602. https://doi.org/10.1001/archpsyc.62.6.593

Kessler RC, Chiu WT, Demler O, Walters EE (2005b) Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Arch Gen Psychiatry 62:617–627. https://doi.org/10.1001/archpsyc.62.6.617

Korhonen T, Latvala A, Dick DM, Pulkkinen L, Rose RJ, Kaprio J, Huizink AC (2012) Genetic and environmental influences underlying externalizing behaviors, cigarette smoking and illicit drug use across adolescence. Behav Genet 42:614–625. https://doi.org/10.1007/s10519-012-9528-z

Kranzler HR et al (2019) Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. Nat Commun 10:1499. https://doi.org/10.1038/s41467-019-09480-8

Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M (2002) Etiological connections among substance dependence, antisocial behavior and personality: modeling the externalizing spectrum. J Abnorm Psychol 111:411–424. https://doi.org/10.1037//0021-843x.111.3.411

Lee JJ et al (2018) Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet 50:1112–1121. https://doi.org/10.1038/s41588-018-0147-3

Liu M et al (2019) Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet 51:237–244. https://doi.org/10.1038/s41588-018-0307-5

Long EC, Verhulst B, Aggen SH, Kendler KS, Gillespie NA (2017) Contributions of genes and environment to developmental change in alcohol use. Behav Genet 47:498–506. https://doi.org/10.1007/s10519-017-9858-y

Maes HH, Sullivan PF, Bulik CM, Neale MC, Prescott CA, Eaves LJ, Kendler KS (2004) A twin study of genetic and environmental influences on tobacco initiation, regular tobacco use and nicotine dependence. Psychol Med 34:1251–1261. https://doi.org/10.1017/S0033291704002405

Mann FD, Briley DA, Tucker-Drob EM, Harden KP (2015) A behavioral genetic analysis of callous-unemotional traits and big five personality in adolescence. J Abnorm Psychol 124:982–993. https://doi.org/10.1037/abn0000099

Mann FD, Patterson MW, Grotzinger AD, Kretsch N, Tackett JL, Tucker-Drob EM, Harden KP (2016) Sensation seeking, peer deviance, and genetic influences on adolescent delinquency: evidence for person-environment correlation and interaction. J Abnorm Psychol 125:679–691. https://doi.org/10.1037/abn0000160

Márquez-Luna C, Gazal S, Loh P-R, Kim SS, Furlotte N, Auton A, Price AL (2019) Modeling functional enrichment improves polygenic prediction accuracy in UK Biobank and 23andMe data sets. bioRxiv:375337. https://doi.org/10.1101/375337

Martin AR et al (2017) Human demographic history impacts genetic risk prediction across diverse populations. Am J Hum Genet 100:635–649. https://doi.org/10.1016/j.ajhg.2017.03.004

Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ (2019) Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet 51:584–591. https://doi.org/10.1038/s41588-019-0379-x

Maurer D (2017) COSTS OF CRIME: experts report challenges estimating costs and suggest improvements to better inform policy decisions. Washington, DC

Meyers JL et al (2013) Interaction between polygenic risk for cigarette use and environmental exposures in the Detroit neighborhood health study. Transl Psychiatry 3:e290. https://doi.org/10.1038/tp.2013.63

Meyers JL et al (2014) Genetic influences on alcohol use behaviors have diverging developmental trajectories: a prospective study among male and female twins. Alcohol Clin Exp Res 38:2869–2877. https://doi.org/10.1111/acer.12560

Middeldorp CM, Lamb DJ, Vink JM, Bartels M, van Beijsterveldt CE, Boomsma DI (2014) Child care, socio-economic status and problem behavior: a study of gene-environment interaction in young Dutch twins. Behav Genet 44:314–325. https://doi.org/10.1007/s10519-014-9660-z

Mills MC, Rahal C (2019) A scientometric review of genome-wide association studies. Commun Biol 2:9. https://doi.org/10.1038/s42003-018-0261-x

National Drug Intelligence Center (2011) National Drug Threat Assessment. www.justice.gov/archive/ndic/pubs44/44849/44849p.pdf

Neale MC, Cardon LR (2013) Methodology for genetic studies of twins and families, vol 67. Springer Science & Business Media, New York

Niv S, Tuvblad C, Raine A, Wang P, Baker LA (2012) Heritability and longitudinal stability of impulsivity in adolescence. Behav Genet 42:378–392. https://doi.org/10.1007/s10519-011-9518-6

Pasman JA et al (2018) GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat Neurosci 21:1161–1170. https://doi.org/10.1038/s41593-018-0206-1

Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164:942–948. https://doi.org/10.1176/ajp.2007.164.6.942

Powell D, Perreira KM, Harris KM (2010) Trajectories of delinquency from adolescence to adulthood. Youth Soc 41:475–502

Quinn PD, Harden KP (2013) Behind the wheel and on the map: genetic and environmental associations between drunk driving and other externalizing behaviors. J Abnorm Psychol 122:1166–1178. https://doi.org/10.1037/a0034426.supp

Reitsma MB et al (2017) Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the global burden of disease study 2015. Lancet 389:1885–1906. https://doi.org/10.1016/S0140-6736(17)30819-X

Rhee SH, Waldman ID (2002) Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. Psychol Bull 128:490–529. https://doi.org/10.1037/0033-2909.128.3.490

Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD (2015) 2010 national and state costs of excessive alcohol consumption. Am J Prev Med 49:e73–e79. https://doi.org/10.1016/j.amepre.2015.05.031

Salvatore JE, Dick DM (2018) Genetic influences on conduct disorder. Neurosci Biobehav Rev 91:91–101. https://doi.org/10.1016/j.neubiorev.2016.06.034

Salvatore JE et al (2014) Polygenic risk for externalizing disorders: gene-by-development and gene-by-environment effects in adolescents and Young adults. Clin Psychol Sci 3:189–201. https://doi.org/10.1177/2167702614534211

Salvatore JE et al (2019) Sibling comparisons elucidate the associations between educational attainment polygenic scores and alcohol, nicotine, and cannabis. Addiction. https://doi.org/10.1111/add.14815

Samek DR, Iacono WG, Keyes MA, Epstein M, Bornovalova MA, McGue M (2014) The developmental progression of age 14 behavioral disinhibition, early age of sexual initiation, and subsequent sexual risk-taking behavior. J Child Psychol Psychiatry 55:784–792. https://doi.org/10.1111/jcpp.12176

Samek DR, Hicks BM, Keyes MA, Iacono WG, McGue M (2016) Antisocial peer affiliation and externalizing disorders: evidence for gene × environment × development interaction. Dev Psychopathol 29:155–172. https://doi.org/10.1017/S0954579416000109

Sanchez-Roige S et al (2018) Genome-wide association study meta-analysis of the Alcohol Use Disorders Identification Test (AUDIT) in two population-based cohorts. Am J Psychiatry. https://doi.org/10.1176/appi.ajp.2018.18040369

Sanchez-Roige S, Fontanillas P, Elson SL, Gray JC, de Wit H, MacKillop J, Palmer AA (2019) Genome-wide association studies of impulsive personality traits (BIS-11 and UPPS-P) and drug experimentation in up to 22,861 adult research participants identify loci in the CACNA1I and CADM2 genes. J Neurosci 39:2562. https://doi.org/10.1523/JNEUROSCI.2662-18.2019

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421. https://doi.org/10.1038/nature13595. https://www.nature.com/articles/nature13595#supplementary-information

Shanahan MJ, Hofer SM (2005) Social context in gene-environment interactions: retrospect and prospect. J Gerontol B Psychol Sci Soc Sci 60:65–76

Tielbeek JJ, Johansson A, Polderman TJ, Rautiainen MR, Jansen P, Taylor M et al (2017) Genome-wide association studies of a broad spectrum of antisocial behavior. JAMA Psychiatry 74(12):1242–1250

Tuvblad C, Grann M, Lichtenstein P (2006) Heritability for adolescent antisocial behavior differs with socioeconomic status: gene-environment interaction. J Child Psychol Psychiatry 47:734–743. https://doi.org/10.1111/j.1469-7610.2005.01552.x

van Beek JHDA et al (2012) Stable genetic effects on symptoms of alcohol abuse and dependence from adolescence into early adulthood. Behav Genet 42:40–56. https://doi.org/10.1007/s10519-011-9488-8

van den Bree MBM, Johnson EO, Neale MC, Pickens RW (1998) Genetic and environmental influences on drug use and abuse/dependence in male and female twins. Drug Alcohol Depend 52:231–241. https://doi.org/10.1016/S0376-8716(98)00101-X

Verhulst B, Neale MC, Kendler KS (2015) The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med 45:1061–1072. https://doi.org/10.1017/S0033291714002165

Verweij KJ et al (2010) Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. Addiction 105:417–430. https://doi.org/10.1111/j.1360-0443.2009.02831.x

Vilhjalmsson BJ et al (2015) Modeling linkage disequilibrium increases accuracy of polygenic risk scores. Am J Hum Genet 97:576–592. https://doi.org/10.1016/j.ajhg.2015.09.001

Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J (2017) 10 years of GWAS discovery: biology, function, and translation. Am J Hum Genet 101:5–22. https://doi.org/10.1016/j.ajhg.2017.06.005

Walters RK et al (2018) Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. Nat Neurosci 21:1656–1669. https://doi.org/10.1038/s41593-018-0275-1

Wertz J et al (2018) Genetics and crime: integrating new genomic discoveries into psychological research about antisocial behavior. Psychol Sci 29:791–803. https://doi.org/10.1177/0956797617744542

Wichers M, Gardner C, Maes HH, Lichtenstein P, Larsson H, Kendler KS (2013) Genetic innovation and stability in externalizing problem behavior across development: a multi-informant twin study. Behav Genet 43:191–201. https://doi.org/10.1007/s10519-013-9586-x

Wojcik GL et al (2019) Genetic analyses of diverse populations improves discovery for complex traits. Nature 570:514–518. https://doi.org/10.1038/s41586-019-1310-4

Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK (2000) Genetic and environmental influences on behavioral disinhibition. Am J Med Genet 96:684–695. https://doi.org/10.1002/1096-8628(20001009)96:5<684::aid-ajmg16>3.0.co;2-g

Steep Discounting of Future Rewards as an Impulsivity Phenotype: A Concise Review

Emily Levitt, Sandra Sanchez-Roige, Abraham A. Palmer, and James MacKillop

Contents

Abstract This chapter provides an overview over the behavioral economic index of impulsivity known as delay discounting. Specifically, delay discounting refers to an individual's preference for smaller immediate rewards over a larger delayed rewards.

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The more precipitously an individual discounts future rewards, the more impulsive they are considered to be. First, the chapter reviews the nature of delay discounting as a psychological process and juxtaposes it with nominally similar processes, including other facets of impulsivity. Second, the chapter reviews the links between delay discounting and numerous health behaviors, including addiction, attention deficit/hyperactivity disorder, and obesity. Third, the determinants of individual variation in delay discounting are discussed, including both genetic and environmental contributions. Finally, the chapter evaluates delay discounting as a potentially modifiable risk factor and the status of clinical interventions designed to reduce delay discounting to address deficits in self-control in a variety of maladaptive behaviors.

Keywords Delay discounting · Impulsivity · Addiction · Substance use disorder · Attention deficit hyperactivity disorder · Obesity

1 Introduction

The concept of impulsivity can be broadly defined as an individual's proneness to act on arising impulses without consideration for the consequences. It is often used as an antonym for a person's capacity for self-control. Belying its conceptual simplicity, however, there is considerable evidence that impulsivity is not a singular psychological trait, but rather is a multidimensional concept, encompassing a number of distinct facets (Evenden 1999; de Wit and Richards 2004). Indeed, impulsivity can be operationalized using a wide variety of behavioral tasks and self-reported measures, and the associations among these vary widely, from substantial overlap to virtually no correlation. As an example, one recent study investigated the latent structure underlying numerous assessments that all nominally measured impulsivity, finding a tripartite latent structure (MacKillop et al. 2016). These three domains comprised (1) multiple assessments of self-reported impulsive personality traits, (2) tasks measuring inhibitory control, and (3) measures of the extent to which a person devalues rewards based on their temporal distance. Although robustly overlapping within each domain, the domains themselves were negligibly associated.

Of these three domains, the phenotype of intertemporal reward preferences is the focus of the current review. There is a long history of investigating variability in preferences for trade-offs between smaller immediate rewards and larger delayed rewards (Ainslie 1975; Mischel 1958), both as a general psychological trait and as a feature of certain health behaviors. These preferences fall within the field of behavioral economics, which integrates concepts and methods from psychology and economics to understand human behavior, particularly in the area of decision-making. In its application to addiction and other psychiatric disorders, behavioral economics combines perspectives from operant learning theory and microeconomics to explain the ways in which individuals make decisions (Bickel et al. 1995; Kirby

and Maraković 1996). Within this framework, preference for smaller immediate rewards over larger delayed rewards (i.e., discounting of delayed rewards or delay discounting [DD]) is a behavioral economic indicator of impulsivity.

1.1 Situating Delay Discounting Among Related Psychological Constructs

Delay discounting can be most concisely defined as the decrease in the subjective value of a reward based on its temporal distance (i.e., how much a reward is discounted based on its delay in time). As such, the greater the devaluation the individual displays (i.e., the more a future reward loses value relative to an immediate reward), the more impulsive that individual is considered (Green et al. 1994; Bickel et al. 1999). Historically, DD was measured using extended decision-making tasks using item batteries that systematically varied the value of the immediate reward and the delay in time after which the larger delayed reward would be available (e.g., Bickel et al. 1999; MacKillop et al. 2006). The most commonly used commodity is money, and three prototypic monetary discounting curves are presented in Fig. 1, illustrating the relationship between the steepness of the curve and the amount that the future reward of $1,000 is discounted. More recently, a

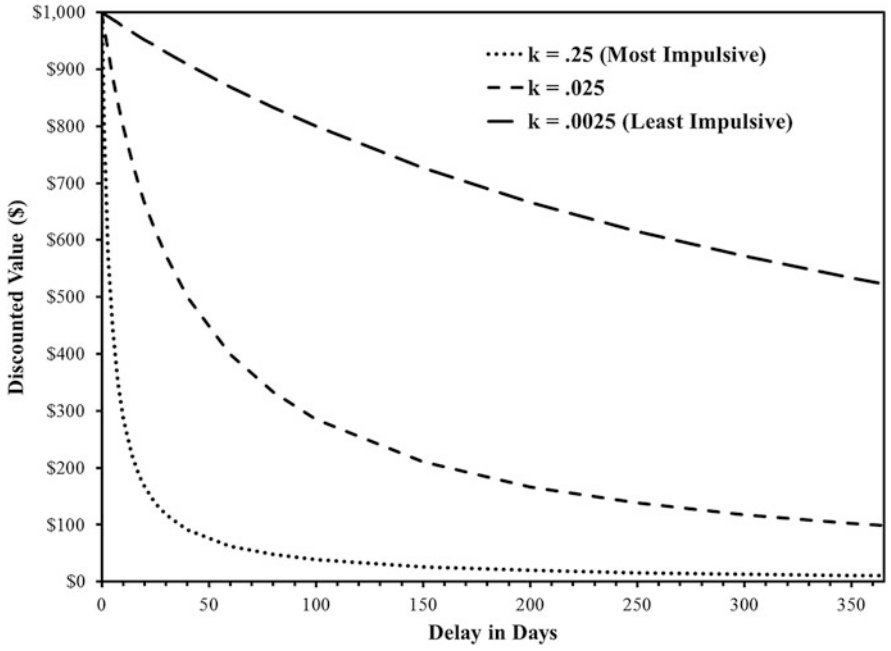

Fig. 1 Prototypic hyperbolic temporal discounting functions at three orders of magnitude

number of shorter measures have been developed, such as the Monetary Choice Questionnaire (MCQ; Kirby et al. 1999) and the Effective Delay 50 measure (ED-50; Koffarnus and Bickel 2014). Both abbreviated measures ask the individual to make specific choices that are yoked to different rates of devaluation to infer a person's overall discounting rate. In the MCQ, for example, individuals are given multiple questions (e.g., *Would you prefer $40 today or $55 in 62 days*?). Similarly, the ED50 asks the individual to choose either the larger reward later or the smaller, sooner reward that is half the value of the larger reward (e.g., *Would you prefer $50 today or $100 in 3 weeks?*). Although the most common commodity used is money, DD tasks can also be implemented for other commodities such as psychoactive drugs or sex or even for health outcomes (Petry 2001; Odum et al. 2002; Johnson and Bruner 2012). Indeed, to enhance ecological validity, some studies have sought to model immediate drug rewards relative to delayed monetary rewards (Amlung and MacKillop 2014). Similarly, the most common form of the task is for rewards, but it can be examined for losses also (Baker et al. 2003), permitting modelling of preferences for smaller losses in the present relative to larger losses in the future, a calculus that is certainly relevant to SUDs. These alternative versions have been implemented much less commonly but nonetheless represent ways the general methodology can be applied to systematically examine decision-making preferences.

The permutations of delay and reward amount in commonly used DD tasks permit discounting curves to be generated, characterizing a person's overall preferences. This is executed by applying a number of different quantitative models of an individual's choice preferences. Most commonly, a hyperbolic single-parameter model is used (Mazur 1987), although hyperboloid two-parameter models have also been proposed (Laibson 1997; Green and Myerson 2004). In these quantitative models, the value of a reward decreases rapidly with immediate or near-term delays and then decreases more slowly as the delay increases. In both cases, hyperbolic models are notably superior to exponential models that presume consistent decreases in subjective value. Alternatively, area under the curve (AUC) can also be calculated to provide an atheoretical measure: The AUC reflects the volume of the discounting curve, with larger areas under the curve reflecting less discounting by the delay time, and therefore less impulsivity (Odum 2011). Another atheoretical alternative is using impulsive choice ratio (ICR) which refers to the raw number of immediate reward choices to the number of delayed reward choices (e.g., Mitchell et al. 2005; Murphy and Mackillop 2012). As such, larger values are associated with greater levels of impulsivity. Model-based approaches are desirable if a linkage to the model's underlying theory is a priority, but model-free approaches may be desirable to avoid assumptions and poor model fit in some cases.

How similar is delay discounting to other psychological assessments of impulsivity? In some cases, DD is quite similar to a number of other decision-making phenotypes, but in other cases quite different, and the similarities and differences are worth identifying. The construct that is most similar is that of delay of gratification (DoG), which typically involves assessing an individual's ability to resist an immediate reward, to obtain a larger reward later (Mischel 1974). A classic example is the

"Marshmallow Task," in which a child is asked to choose between one marshmallow in front of them and two marshmallows if she/he waits for an indeterminate amount of time (Mischel et al. 1989). In both cases, DD and DoG operationalize self-control as orientation to larger future rewards, but some meaningful differences are present. Specifically, DD is typically administered as a decision-making task, with multiple items to reflect different permutations of preferences and explicit descriptions of values and delays, whereas behavioral DoG paradigms use a single choice or a small number of choices (e.g., Mischel et al. 1989). In these in vivo assays, DoG tasks are procedures in which an individual is in the presence of an immediate reward, such as the marshmallow, and has to resist the alternative in real time. As such, DoG tasks also incorporate temptation (including the extent to which it is elicited) and a person's ability to then directly resist the elicited desire. In contrast, DD tasks are relatively narrower assays of how the imposition of a delay affects the value of a reward. Moreover, the individual in the DoG task does not know the amount of time required to wait for the reward, incorporating an element of uncertainty and probability, whereas the delay in time is explicitly expressed in the DD task. In some ways, a task called the experiential discounting task (EDT) bridges this gap by using the experimental methods of traditional DD tasks with relatively short in vivo delay periods (Reynolds and Schiffbauer 2004). Performance on the EDT also includes a probabilistic dimension, not just delay, and has not been found to closely correspond with performance on traditional DD measures (Smits et al. 2013). Fundamentally, although there is close conceptual overlap between DD, DoG, and the EDT, there are meaningful differences among the measures.

Another related decision-making phenotype is probability discounting (PD), usually considered a measure of risk orientation. More specifically, PD refers to the extent to which a person devalues (discounts) a reward as a function of the likelihood of its occurrence decreases (Richards et al. 1999). In PD tasks, participants choose between certain and probabilistic rewards, both provided immediately. For example, an individual might choose between a 75% chance for $10 and $5 that is guaranteed (100% chance). Thus, the measure assesses risk orientation in trade-offs between larger probabilistic and small guaranteed outcomes. In other words, it is a measure of how the individual balances potential reward over the potential loss. Although there are clear conceptual and methodological similarities, DD and PD are fundamentally distinct, with one measuring regulation of the impulse for an immediately available reward (DD) and the other measuring willingness to accept risk for a larger reward (PD). Several studies have shown that these measures are only modestly to moderately correlated (e.g., Jarmolowicz et al. 2012; MacKillop et al. 2015a).

In addition to PD tasks, other behavioral tasks assay risk orientation. For example, the Balloon Analogue Risk Task (BART) (Lejuez et al. 2003) asks the individual to pump a hypothetical balloon with air, and with each pump the individual receives more money. However, if the balloon becomes too inflated, it "explodes" and all of the money for that trial is lost. Thus, with each additional pump, there is greater reward but also greater risk of loss. Another common measure of risk taking is the Iowa Gambling Task (IGT) (Bechara et al. 1994). Here, the individual is asked

to make choices from four electronic decks of cards, with each deck having a different schedule of gains and losses. Some decks have value outcomes but lead to more losses overall, whereas others have medium-sized rewards but fewer losses overall. Performance is measured in overall winnings across 100 trials, reflecting the extent to which participants learn the schedules and select from the most advantageous deck. The BART and IGT are fundamentally measures of risk to the extent that they assay trade-offs between probabilistic outcomes, more akin to PD, not DD.

How does delay discounting relate to the other major domains of impulsivity, impulsive action (behavioral inhibition) and self-reported impulsive personality traits. In the first case, behavioral inhibition, also referred to as impulsive action, broadly refers to a person's ability to inhibit a potent arising motor response. In other words, these tasks determine if the individual is able to suppress already planned actions (Bari and Robbins 2013). The two most common measures of response inhibition are the Go/No Go task and the Stop Signal Task (Fillmore and Weafer 2013). In the former, the individual emits a response during frequent "Go" trials, but has to occasionally refrain from responding during the "No Go" trials. In the latter, the individual is instructed to respond to a stimulus (e.g., an arrow), but, in some instances, the trial is interrupted by a signal to stop, such as an auditory tone, after the initial stimulus is presented. In both cases, behavioral inhibition tasks operationalize impulsivity by capacity to gate potent arising motor responses, a process that is clearly distinct from DD.

With regard to impulsive personality traits, impulsivity can also be explored as a psychological trait through self-reported questionnaires. Early measures focused on self-perceptions of impulsivity as unitary (Eysenck and Eysenck 1978), but more recent measures have multiple subscales that fractionate impulsivity into different facets (Patton et al. 1995; Whiteside and Lynam 2001). One commonly used self-report measure is the UPPS-P Impulsive Behavior Scale, which measures five aspects of impulsivity: premeditation, perseverance, sensation seeking, and positive and negative urgency (Whiteside and Lynam 2001). Another commonly used measure is the Barratt Impulsiveness Scale, which encompasses three domains of impulsivity: attentional, motor, and nonplanning impulsivity (Patton et al. 1995). These measures and their subscales have been linked to substance use disorders and a variety of other health behaviors (for a review, see Miller and Lynam 2013), but are weakly associated with DD (e.g., MacKillop et al. 2014).

2 Impulsive Delay Discounting and Health

Delay discounting (DD) has been associated with numerous psychiatric disorders and health behaviors, including substance use disorders (SUD), attention-deficit/hyperactivity disorder (ADHD), obesity, and mood disorders (Bickel et al. 2014; MacKillop et al. 2011; Pulcu et al. 2013; Xia et al. 2017; Stojek and MacKillop 2017). The following section will address the level of evidence in the context of these specific disorders.

2.1 Addiction

In some ways, impulsive DD can be thought of as pathognomonic of addictive behavior, in the sense that the person is exhibiting a preference for the immediate effects of a drug over the long-term benefits from abstaining. Impulsive DD can also provide insight into self-control failures, such as lapses and relapse following treatment, another common characteristic of addictive behavior (Lowman et al. 1996). Within the context of behavioral economics, self-control failures are described as preference reversals (i.e., an individual alternating between the decision to use or not use, changing their preference from not using a substance to resuming use). This is particularly relevant to DD because hyperbolic DD preferences predict preference reversals as access to a reward becomes close (Ainslie 1975). Many studies have therefore explored DD to help elucidate these essential concepts in addiction.

Numerous studies have used case-control designs to examine the differences in DD tasks between SUD+ individuals and control groups of matched participants. Findings from these studies indicate significantly higher levels of DD in individuals with alcohol use disorder (Vuchinich and Simpson 1998; Mitchell et al. 2005; Bobova et al. 2009), nicotine dependence (Bickel et al. 1999; Odum et al. 2002; Johnson et al. 2007), opiate dependence (Madden et al. 1997; Kirby and Petry 2004), and cocaine dependence (Allen et al. 1998; Coffey et al. 2003; Heil et al. 2006). This pattern was also found to be consistently present in a meta-analysis of case-control studies (MacKillop et al. 2011), comparing individuals who exceeded a criterion for addictive behavior ("cases") to matched comparison participants ("controls"). This meta-analysis indicated a medium effect size difference overall and a significantly larger difference for studies that used a clinical criterion for characterizing the case group. More recently, a meta-analysis of studies using dimensional designs (i.e., studies examining continuous associations between DD and severity of addictive behavior) reported a similarly consistent association between DD and addictive behavior and a larger association with clinical indicators of severity (Amlung et al. 2017).

2.2 Attention Deficit/Hyperactivity Disorder

Impulsive decision-making is a fundamental symptom in individuals with ADHD (Still 2006), and numerous investigations have reported that individuals with ADHD have been found to exhibit higher rates of DD compared to healthy controls (Sonuga-Barke et al. 1992; Barkley et al. 2001; Hurst et al. 2011; Demurie et al. 2012). A recent meta-analysis of case-control studies showed that individuals with ADHD had higher DD rates ($d = 0.43$), with no evidence of systematic differences based on age or task outcome (real or hypothetical). Of note, there may be differences in the degree of DD based on ADHD subtypes (Scheres et al. 2010), namely,

ADHD-inattention and ADHD-combined type. For example, DD was higher in individuals with ADHD-combined, but not ADHD-inattention. DD may therefore be implicated in the impulsivity/hyperactivity dimension of ADHD but not in the inattention subtype.

2.3 Obesity and Eating Disorders

Akin to SUD, obesity can be considered a disorder of overconsumption. There are many parallels between obesity/overeating and SUD (list a couple of reviews on this topic). For example, studies have revealed that high-palatability foods that are high in sugar, fat, and salt have neurobiological effects that are similar to those of addictive drugs (Kenny 2011). Consistent with this view, a number of studies report that individuals who are overweight or obese tend to show greater DD compared to healthy-weight individuals (Stojek and MacKillop 2017), and a recent meta-analysis found a significant, medium effect size association between steeper discounting and body mass index (Amlung et al. 2016). There have also been several studies examining DD in the context of eating disorders. One investigation found higher rates of DD in women who were obese and diagnosed with binge eating disorder (BED) compared to women who were obese with no diagnosis and healthy controls (Manwaring et al. 2011), but others have not found BED is differentiating (Davis et al. 2010; Mole et al. 2015). Of note, however, a recent study found that food addiction (i.e., compulsive eating with behavioral features that parallel substance use disorders) statistically mediated the relationship between DD and obesity (VanderBroek-Stice et al. 2017), which specifically links DD to obesity by way of its association with compulsive behavior.

Intriguingly, a number of studies have reported significantly *decreased* levels of DD in individuals with anorexia nervosa (AN) compared to healthy controls (Steinglass et al. 2012). This appears to reflect excessively high self-control in individuals who have AN. Other studies have found no difference between individuals who are in remission from AN and healthy controls (Ritschel et al. 2015) and that individuals with AN discounted more steeply than healthy controls pre-treatment, but, after weight restoration, there was no difference between the two groups (Decker et al. 2015). Thus, excessive overvaluation of the future appears to be restricted to the active phase of the illness. These findings suggest that DD maps onto both disorders of insufficient self-regulation and excessive self-regulation.

2.4 Suicidality

Although the determinants of suicide are highly multifarious, it is nonetheless often thought of as an impulsive act. Specifically, suicide may be considered an impulsive decision to end the individual's suffering in the present, with insufficient

consideration of the future. This perspective is supported empirically by evidence that individuals who have made suicide attempts score higher on DD tasks than healthy controls (Cáceda et al. 2014). In another study, Dombrovski et al. (2011) compared older adults who either had depression and attempted suicide or had depression but no history of suicide attempts or ideation. Individuals with suicide attempts displayed significantly more impulsive DD compared to individuals with no attempts; however, individuals who planned their suicide attempts were less impulsive DD. In a study of adolescents, the girls with multiple suicide attempts scored significantly higher on DD tasks than a control group (Mathias et al. 2011). However, an association between suicide attempts and DD has not been present in all studies (e.g., Bridge et al. 2015), suggesting it is not necessarily a consistent feature and may be specific to certain subtypes of suicidality (e.g., non-planful attempts).

2.5 Major Depressive Disorder

Individuals with depression may also discount more steeply than healthy controls. Pulcu et al. (2014), for example, found that individuals with depression as compared to healthy controls demonstrated significantly higher rates of DD. Moreover, even after controlling for depression severity, those with lower psychosocial functioning and higher hopelessness severity discounted more steeply than all other participants. Preclinical studies have also observed increased DD in rodents with lower serotonin levels (Schweighofer et al. 2008), which is notable because serotonin reuptake is the target of many antidepressant drugs. One study reported that individuals with increased anhedonia, a common symptom of depression, demonstrated *decreased* levels of DD compared to individuals with lower levels of anhedonia. Thus, impulsive DD appears to be associated with MDD in general, but the relationship may be more complex and require consideration of anhedonia also.

2.6 Schizophrenia

A number of studies suggest that individuals with schizophrenia discount rewards at greater rates than healthy controls (Heerey et al. 2007, 2011; Ahn et al. 2011; Gold et al. 2013; Weller et al. 2014; Yu et al. 2017). However, another study examined DD in cigarette smokers with and without schizophrenia and found no difference in DD between the two groups (MacKillop 2013). This suggests a potentially confounding issue when studying DD in individuals with schizophrenia, since cigarettes smoking is much higher in patients with schizophrenia, meaning that higher rates of DD could be related to tobacco involvement rather than schizophrenia per se.

2.7 Related Health Behaviors

Steeper discounting has been associated with a number of other important health behaviors. Daugherty and Brase (2010), for example, found that DD was significantly associated with lack of exercise and risky behavior, for example, not wearing a seat belt or not wearing sunscreen. Moreover, higher discounting was associated with significantly lower rates of mammography and pap smears for women and prostate exams for men, as well as dental visits, cholesterol visits, flu shots, and less engagement in positive healthy habits (Bradford 2010). Individuals with higher discounting rates have also demonstrated a decreased likelihood of checking blood pressure and not changing their diet and exercise habits when diagnosed with hypertension (Axon et al. 2009). Similarly, higher rates of DD have been associated with sexual risk-taking behavior defined as earlier age of first sexual experience and relationship infidelity (Reimers et al. 2009; Jones et al. 2018; Lawyer and Mahoney 2018). In a sample of hazardous drinkers from an emergency department, increased rates of DD were significantly related to sexual risk-taking during drinking episodes (MacKillop et al. 2015a). Furthermore, individuals who both discounted more steeply and had positive sex-related alcohol expectancies were significantly more likely to engage in risky sexual behavior (Celio et al. 2016).

Finally, similar to anorexia nervosa, obsessive-compulsive personality disorder (OCPD), a condition that is characterized by excessive self-control, has been associated with an enhanced ability to delay rewards in favor of future rewards (Pinto et al. 2014). This represents a second domain where a psychiatric condition is associated with excessive self-control as measured by DD.

2.8 Impulsive Delay Discounting as a Trans-diagnostic Mechanism

The pattern of associations with multiple psychiatric disorders and health outcomes reviewed above suggest that impulsive DD may be thought of as a trans-diagnostic process in psychiatric disorders and other conditions that involve self-regulation. As a psychological phenotype, it exists as a continuous, dimensional trait across the population, but either excessively high or excessively low DD is associated with conditions of self-regulatory under-control or over-control, respectively. This theoretical relationship is shown in Fig. 2, depicting DD as a continuous trait with an adaptive significance that follows an inverted U-shaped curve. Very low levels of future discounting, reflecting over-control, are maladaptive. Moderate levels are adaptive, reflecting healthy preferences between smaller immediate rewards and larger delayed rewards. However, high discounting of future rewards becomes maladaptive, reflecting an unhealthy focus on immediate rewards. Notably, the Gaussian form of the curve is intentional as it reflects the distribution of DD across the population, with most people falling within a normative range but small numbers of individuals exhibiting excessively high or low levels.

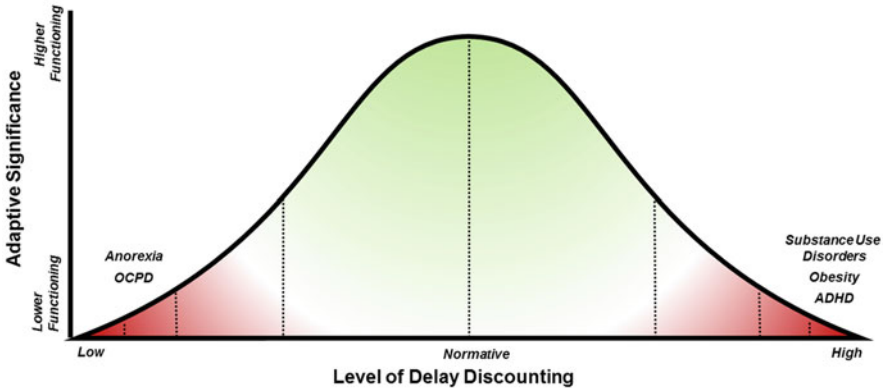

Fig. 2 The conceptual relationship between adaptive significance and delay discounting as a trans-diagnostic process. Delay discounting is a dimensional psychological trait, varying from very low to very high levels of future discounting, that generally follows a Gaussian distribution across the population. The adaptive significance conforms to an inverted U-shaped curve, with excessively low or excessively high levels of future discounting being associated with maladaptive outcomes. Note: *ADHD* attention deficit hyperactivity disorder, *OCPD* obsessive-compulsive personality disorder

Consistent with the notion of DD as a trans-diagnostic factor, it is included in the National Institute on Mental Health Research Domain Criteria initiative (Insel et al. 2010). This initiative seeks to improve the understanding, diagnosis, and treatment of mental disorders by situating them among objective, empirically based, biobehavioral indicators that are relevant across different psychiatric conditions. Within this framework, DD is considered part of the Positive Valence Systems domain, in the Reward Valuation construct, reflecting the subconstruct of Delay. To date, identifying valid trans-diagnostic indicators has proved challenging, and given the substantial evidence linking excessively high and low levels to a variety of different health behaviors, DD may be one of the most successful (Lempert et al. 2019).

3 Determinants of Impulsive Delay Discounting

Given the links between steep discounting of future rewards and a multitude of negative health outcomes, this section addresses the putative causes of variation in DD and the extent to which it is a determinant of health, as opposed to a consequence.

3.1 Genetic Determinants of Impulsive Discounting

There is increasing evidence that individual differences in impulsive discounting are partially determined by innate genetic variation and that DD may serve as a

behavioral mechanism that explains the link between genetic variation and subsequent risk for adverse health outcomes. Specifically, DD is a candidate endophenotype for the preceding health outcomes, meaning that it is a heritable, generally stable characteristic that may be used to clarify how genetic factors contribute to risk for a condition (for reviews, see MacKillop 2013; Gray et al. 2019).

Evidence for genetic influences on DD comes from a number of lines of inquiry. In preclinical studies, significant strain differences are present for DD (Anderson and Woolverton 2005; Madden et al. 2008; Anderson and Diller 2010). This is important because inbred strains are largely isogenetic within strains, so systematic strain-based differences imply a genetic basis. Furthermore, these differences are observed in animals that have no exposure to psychoactive drugs, eliminating the potential confound of drug effects that is present in most human studies. However, although it is highly advantageous for DD to be able to be modelled using infrahuman species, it is also important to note that the phenotype in preclinical models differs in important ways from the common human DD measures. Specifically, DD appears to be more difficult for rodents, requiring the delayed rewards to have very short time scales and in vivo time delays. In humans, twin studies have indicated moderately high heritability of DD (Anokhin et al. 2011; Isen et al. 2014). For example, Anokhin et al. (2014) identified that DD was 57% heritable, with a notable increase in the heritability as the individuals aged from 16 to 18. Obliquely related, a number of studies have found that family history of SUD, an established risk factor for addiction that partially reflects genetic factors, is also associated with individual levels of DD (Dougherty et al. 2014; Vanderbroek et al. 2016).

Candidate gene studies are genetic studies that typically focus on one or a few genetic variants that are in or near genes for which there is a strong biological rationale. Although candidate gene studies are increasingly considered unreliable because they often do not have sufficient statistical power to detect the small effect sizes that are biologically most probable (e.g., Hart et al. 2013), they nevertheless have been used to study DD. Many of these studies focus on genes involved in dopamine neurotransmission, such as *COMT*, *ANKK1*, and *DRD4* (for a review, see Gray et al. 2019). For example, a single nucleotide polymorphism (SNP; rs1800497) in *ANKK1* that has been implicated in dopamine D_2 receptor density has been associated with DD in samples of university students and smokers (Eisenberg et al. 2007; MacKillop et al. 2015b). In another study, individuals with lower socioeconomic status (SES) who had the 7-repeat version of a VNTR polymorphism within *DRD4*, which encodes the dopamine D_4 receptor, were significantly more likely to steeply discount future rewards than low-SES individuals who had no copies of the 7-repeat allele (Sweitzer et al. 2013). However, these candidate gene findings have not been replicated in larger studies that should have been well powered to detect the association, had the original finding been accurate.

There have been two genome-wide association studies (GWAS) of DD to date. The first used 23,127 research participants from the consumer genomics company 23andMe and assessed DD using the Monetary Choice Questionnaire (MCQ; Kirby et al. 1999) to estimate hyperbolic temporal discounting functions. They found a genome-wide significant association between a single nucleotide polymorphism in

the *GPM6B*, which encodes a protein that controls the internalization of the serotonin transporter. They replicated this finding in an independent sample of 928 individuals collected by Genes for Good. They estimated SNP heritability at 12% (Sanchez-Roige et al. 2018) and showed significant genetic correlations with multiple phenotypes that had been previously associated with DD in nongenetic studies, including ADHD, smoking (positively with ever smoked and daily cigarettes, and negatively for successful quitting), and obesity. Notably, none of the previously reported candidate genes findings were replicated in this study, despite the much larger and presumably more powerful sample size. In the second GWAS study, MacKillop et al. (2019) examined 986 healthy young adults who were carefully screened against significant substance use and abuse to avoid the potentially confound effects of substance use on DD. These subjects were tested for DD under carefully controlled laboratory conditions using the MCQ and analyzed in a manner that was similar to Sanchez-Roige et al. (2017). That study found modest evidence in support of a previously implicated SNP (rs521674) and found a genome-wide significant association for a variant on chromosome 2; however, this locus is in an intergenic region of unknown functional significance and was not supported by the larger study of Sanchez-Roige et al. (2017). On balance, although there is relatively strong evidence that DD is genetically influenced, even larger sample sizes will be needed to identify variants that mediate these heritable differences.

3.2 Environmental Factors

Beyond innate genetic variation, environmental factors may also play a critical role in impulsive DD. The most obvious of these is substance use itself (or the other unhealthy behaviors with which it is linked) causing impulsive delay discounting, rather than the other way around. From this perspective, DD can be thought of as a symptom, rather than a cause. In animal models, there is some evidence that protracted exposure to psychoactive drugs gives rise to more impulsive discounting (Mendez et al. 2010; Mitchell et al. 2014). On the other hand, there is also evidence in preclinical models that DD prior to substance use predicts acquisition and progression of self-administration (Perry et al. 2005; Anker et al. 2009). In addition, there is evidence that impulsive DD predates substance use or other adverse outcomes and predicts progression (Audrain-McGovern et al. 2009; Fernie et al. 2013; Kim-Spoon et al. 2019; Lee et al. 2017), suggesting that DD can be both a risk factor and a consequence.

There is also evidence that adverse environmental exposures, particularly stressful life events, give rise to more impulsive DD. In animal studies, for example, rats experiencing acute stress exhibit significantly steeper DD than a control group, an effect that was reversed by a dopamine antagonist (Shafiei et al. 2012). In human studies, adolescent's self-reports of parental inconsistency were significantly related to steeper discounting and alcohol use (Schneider et al. 2014). In addition, early life stress, as measured by adverse childhood experiences (ACEs), was found to be

associated with steeper DD in adulthood (e.g., Lovallo 2013). Furthermore, Oshri et al. (2018) found that impulsive DD partially mediated the relationship between childhood adversity and adult substance use. Similarly, there is evidence that parental DD predicted longitudinal changes in offspring DD based on the level of perceived household chaos (e.g., arguments, instability, or discord; Peviani et al. 2019).

Another environmental factor posited by investigators is the influence of low socioeconomic status on DD. Indeed, it is logical for individuals in more precarious financial circumstances to choose the smaller sooner reward simply out of an acute need of the money for specific purposes, unlike more economically stable individuals. In particular, individuals who grew up in resource-poor families were more likely to discount future rewards, in favor of immediate smaller rewards, compared to those who grew up with access to more resources (Griskevicius et al. 2011). Similarly, individuals in countries with lower life expectancies were significantly more likely to demonstrate impulsive DD than individuals from countries with greater life expectancies (Griskevicius et al. 2011; Lee et al. 2018).

Adversity broadly comprises a variety of both negative exposures (e.g., abuse, household discord) and psychosocial privations (e.g., divorce, parental incarceration, or neglect). Multiple studies have implicated impulsive DD to exposure to traumatic life events (e.g., Van Den Berk-Clark et al. 2018). For example, in a sample of elderly participants with and without a history of childhood trauma, those who were trauma-exposed were significantly more likely to steeply discount future rewards than the unexposed control group (Simmen-Janevska et al. 2015). Similarly, Li et al. (2011) observed an increase in DD in individuals directly exposed to violent events compared to those that were not. In a very unique design, DD assessments were administered prior to and following an earthquake in China, demonstrating significantly enhanced preferences for smaller, sooner rewards following the disaster.

These diverse findings linking aspects of adversity, stress, and trauma to DD can be understood in a number of ways. One explanation is that the link to more impulsive DD can be understood as simply one more negative consequence of these antecedents (e.g., depression). An alternative explanation is the application of life history theory, which situates psychological traits within an evolutionary framework that seeks to maximize fitness (Copping et al. 2014; Del Giudice et al. 2015). Specifically, individuals who have minimal resources are theorized to have a "fast" life history strategy, learning to take what they can immediately acquire (i.e., a smaller reward sooner). In contrast, individuals who have access to more resources putatively have a slower life history strategy and thus are more likely to wait for larger rewards later. From this perspective, exposure to adversity may accurately signal a more dangerous and unpredictable environment in which one needs to act in the present or may not have the opportunity to reap future rewards. Under those circumstances, a "bird in the hand" may well be worth more than "two in the bush." In other words, the smaller sooner reward may be adaptive in risky, unreliable, or otherwise perilous circumstances. Greater orientation to immediate reinforcers may

become maladaptive, however, if an individual develops a fast life history strategy that exerts its influence far beyond the window of utility.

3.3 Delay Discounting as a Recursive Etiological Process

Of course, truly demonstrating causality of DD in relation to health outcomes cannot be done in any single study. It may be the case that individuals develop high DD from exposure to early life stress; however, it may also be the case that these individuals already had a genetic vulnerability to more impulsive DD, before even being exposed to adversity. While studies have demonstrated both genetic and environmental determinants of impulsivity, it may be more likely that impulsive discounting ultimately reflects a psychological process that is a product of both "nature" and "nurture," or what has been referred to as a recursive etiological process (MacKillop 2013). For example, a person might have a high genetic predisposition for more impulsive DD but unfortunately also be exposed to substantial childhood stress, producing even greater impulsivity. In turn, such a combination would putatively increase the seeking out particular experiences, including substance experimentation and persistent use, which, in turn, may further adversely affect DD preferences. Finally, substance use and other high-risk behaviors may result in traumatic exposures (e.g., physical or sexual assault, motor vehicle accidents), which may further exacerbate DD and ongoing substance use. Rather than trying to disentangle definitively whether impulsive DD is predominantly a cause or consequence, it may be most trenchant to recognize that it is a psychological trait that has an evolving and unfolding influence over the lifespan.

4 Is Impulsive Delay Discounting a Viable Treatment Target

Given the evidence robustly linking impulsive DD to psychopathology and other negative health outcomes, targeting DD as part of a treatment intervention may be a useful clinical strategy. To date, three broad strategies have been undertaken: pharmacotherapies, behavioral strategies, and, most recently, neuromodulation.

4.1 Pharmacotherapies

Many studies have examined the direct effects of pharmacological manipulations on DD. In a comprehensive review, Perkins and Freeman (2018) identify various drugs tested that may reduce DD. The most commonly cited pharmacological treatment of

ADHD and other disorders is D-amphetamine (D-AMPH), a psychostimulant that augments the concentration of dopamine in the striatum and norepinephrine in the prefrontal cortex. In fact, administration of D-AMPH has been observed to decrease DD in healthy subjects (de Wit et al. 2002). However there has been inconsistency in these findings, possibly due to the variability in dosage and routes of administration (Winstanley 2011). Another psychostimulant implicated in reduced rates of DD is methylphenidate. For example, administration of methylphenidate in children was found to decrease DD using real rewards, but had no effect on tasks using hypothetical rewards (Shiels et al. 2009). Moreover, adults with a criminal background, but no history of ADHD, demonstrated decreased DD following acute administration of methylphenidate (Pietras et al. 2003). Modafinil, another monoamine agonist, has also been shown to reduce DD (Ashare and McKee 2012; Schmaal et al. 2014). Beyond psychostimulants, other medications have also been investigated in relation to DD, including atomoxetine, a norepinephrine reuptake inhibitor (Robinson et al. 2008; Sun et al. 2012), and naltrexone, an opioid receptor antagonist (Boettiger et al. 2009; Mitchell et al. 2007), although these findings have either been restricted to preclinical models or largely inconsistent.

4.2 Behavioral Strategies

Applying behavioral interventions designed to reduce DD may be a viable clinical strategy to reverse-engineer the risk conferred by impulsive discounting and has been investigated in an increasing number of studies. In a recent systematic review and meta-analysis on behavioral manipulations used to decrease DD, 92 studies were identified and divided into 9 different intervention categories (Rung and Madden 2018). The results of the review demonstrated that, in general, the behavioral? interventions significantly reduced DD. However, the majority of the studies were laboratory manipulations, not clinical interventions, demonstrating that DD is amenable to modification, but not necessarily that the effects are persistent and ultimately contribute to positive behavior change. Furthermore, where the studies did include clinical interventions, DD was typically an outcome variable and was not used as a direct focus for the intervention, again generating obliquely supportive evidence.

One particularly promising method is episodic future thinking (EFT), defined as using a structured protocol to vividly imagine positive events in one's future. Using this approach, a number of studies have suggested that imagining positive future events helps to enhance the value of that event, making the individual less likely to choose the smaller immediate reward. Indeed, ten studies were identified in the recent review that show a significant decrease in DD as a result of EFT intervention. For example, EFT was found to decrease DD and cigarette smoking compared to a control group (Stein et al. 2016, 2018), as well as decrease alcohol consumption (Bulley and Gullo 2017). EFT was also associated with a decrease in DD for food rewards in overweight and obese women (Daniel et al. 2013). Implementing EFT for individuals with a propensity for impulsive DD is arguably the most promising

adjunctive strategy for addressing impulsive DD in the treatment of SUDs and related health behaviors.

Other strategies implicated in reducing impulsive DD include learning-based approaches, such as reward bundling and delay/fading exposures. Reward bundling refers to the notion that when rewards are bundled together, the overall value exceeds the immediate value of any single one. A larger delayed reward is cognitively not just that single reward, but is representative of a general strategy toward rewards that confer greater aggregated value. In normative decision-making, reward bundling is proposed to be the reason why our preferences are not always overcome by the hyperbolic increase in value as a reward becomes imminent. As a clinical strategy, reward bundling refers to deliberately exposing people to larger delayed rewards to reveal the value of the larger-later strategy and generate reward bundling in the individual. In other words, by providing the individual with a succession of delayed rewards, it may become more apparent to them that the lower sum is less valuable than the larger sum. For example, individuals who were regular smokers significantly preferred larger-later rewards when the rewards were grouped together, whereas nonsmokers did not show this pattern (Hofmeyr et al. 2010). Moreover, individuals who received five rewards delivered in succession were significantly more likely to change their initial preference from smaller rewards sooner to larger rewards later (Kirby and Guastello 2001). In animal studies, rats significantly preferred the larger reward later when the reward was given three times in succession, as opposed to when the reward was delivered in a single occurrence (Ainslie and Monterosso 2003). Similarly, rats were given bundles of either one, three, or nine rewards, demonstrating a significant choice preference for larger-later rewards in the nine bundle group, compared to those unbundled rewards (Stein et al. 2013). It is possible then that changing the individual's perception to allow them to view a whole set of rewards and consequences may facilitate changes in impulsive decision-making.

Additionally, delay fading/exposure, designed to gradually fade out certain behaviors, may be another strategy to reduce impulsive DD. One of the earliest animal studies implementing this technique by Mazur and Logue (1978) demonstrated that progressively increasing the delay between the smaller and larger rewards in pigeons resulted in a greater preference for the larger delayed reward. Similarly, children who frequently selected the smaller sooner reward were more likely to switch their pattern to larger delayed rewards when exposed to multiple fading sessions consisting of gradual increases in the delay between rewards (Schweitzer and Sulzer-Azaroff 1988). This is another instance of exposing individuals to specific contingencies that reinforce larger-later value preferences. In both cases, the studies to date have primarily demonstrated proof of concept that DD can be affected by the protocol but have not demonstrated that these are strategies that are ready for clinical implementation.

4.3 Neuromodulation

The newest strategy for reducing impulsive DD is neuromodulation, which refers to attempts to directly affect brain activity as a therapeutic strategy. In particular, studies have explored transcranial magnetic stimulation (TMS), a noninvasive technique that uses a magnetic field to modify brain activity. One region of the brain that has been most commonly studied is the dorsolateral prefrontal cortex (dlPFC), which has been consistently implicated in impulsive DD (Owens et al. 2019). Moreover, increasing activity in the left, but not the right, dlPFC, producing an excitatory effect, has been demonstrated to decrease DD (Sheffer et al. 2013). Similarly, Figner et al. (2010) inhibited activity in the left, but not the right, dlPFC using low-frequency stimulation and found an increase in impulsive DD. Unfortunately, however, other findings on targeting the dlPFC via neuromodulation to affect DD have been mixed. For example, one study examined pathological gamblers, finding no reductions in rates of DD after TMS of the dlPFC, although there were significant decreases in subjective motivation and physiological reinforcing effects of gambling (Hecht et al. 2013). Furthermore, in contrast to the aforementioned studies, inhibition of the right dlPFC was associated with a decrease in impulsive DD in two studies (Cho et al. 2010, 2012). Another area potentially implicated in impulsive DD is the medial prefrontal cortex (MePFC), associated with dopaminergic neurotransmission. Moreover, excitation of the MePFC via TMS was found to decrease impulsive DD and reduce dopamine release in the dorsal striatum (Cho et al. 2015).

In contrast to TMS, transcranial direct-current stimulation (tDCS) uses low electric current delivered through two electrodes placed on the scalp. The current can either be anodal or cathodal, generating excitatory or inhibitory responses, respectively. One study observed increased DD from anodal tDCS to the left dlPFC and cathodal tDCS to the right dlPFC (Hecht et al. 2013). In direct contrast, another study found that anodal stimulation of the left dlPFC decreased DD, and cathodal stimulation of the left dlPFC increased DD (Shen et al. 2016). Thus, the potential for tDCS as a clinical strategy to reduce impulsive DD remains in its infancy.

5 Conclusions

In sum, impulsive DD is a specific form of impulsivity that has been linked to a wide variety of health outcomes related to self-regulatory capacity. It has been most prominently studied in relation to SUDs, but it has also been linked to other psychiatric conditions and maladaptive behaviors. As a phenotype, DD is determined by both genetic and environmental influences, and understanding the relative influence of the “nature” and “nurture” components of DD is a high priority for the field. Importantly, although DD within an individual is generally stable, it may also

vary in response to contextual, emotional, or physiological conditions. Both the stable trait and the fluctuations in DD over time provide a novel and potentially important target for clinical intervention to reduce the numerous negative health outcomes associated with this key aspect of self-regulation.

References

Ahn WY, Rass O, Fridberg DJ, Bishara AJ, Forsyth JK, Breier A et al (2011) Temporal discounting of rewards in patients with bipolar disorder and schizophrenia. J Abnorm Psychol 120(4):911

Ainslie G (1975) Specious reward: a behavioral theory of impulsiveness and impulse control. Psychol Bull 82:463–496

Ainslie G, Monterosso JR (2003) Building blocks of self-control: increased tolerance for delay with bundled rewards. J Exp Anal Behav 79:37–48

Allen TJ, Moeller FG, Rhoades HM, Cherek DR (1998) Impulsivity and history of drug dependence. Drug Alcohol Depend 50(2):137–145

Amlung M, MacKillop J (2014) Understanding the effects of stress and alcohol cues on motivation for alcohol via behavioral economics. Alcohol Clin Exp Res 38:1780–1789

Amlung M, Petker T, Jackson J, Balodis I, MacKillop J (2016) Steep discounting of delayed monetary and food rewards in obesity: a meta-analysis. Psychol Med

Amlung M, Vedelago L, Acker J, Balodis I, MacKillop J (2017) Steep delay discounting and addictive behavior: a meta-analysis of continuous associations. Addiction 112

Anderson KG, Diller JW (2010) Effects of acute and repeated nicotine administration on delay discounting in Lewis and Fischer 344 rats. Behav Pharmacol 21:754–764

Anderson KG, Woolverton WL (2005) Effects of clomipramine on self-control choice in Lewis and Fischer 344 rats. Pharmacol Biochem Behav 80:387–393

Anker JJ, Perry JL, Gliddon LA, Carroll ME (2009) Impulsivity predicts the escalation of cocaine self-administration in rats. Pharmacol Biochem Behav 93:343–348

Anokhin AP, Golosheykin S, Grant JD, Heath AC (2011) Heritability of delay discounting in adolescence: a longitudinal twin study. Behav Genet 41:175–183

Anokhin AP, Grant JD, Mulligan RC, Heath AC (2014) The genetics of impulsivity: evidence for the heritability of delay discounting. Biol Psychiatry 77:887–894

Ashare RL, McKee SA (2012) Effects of varenicline and bupropion on cognitive processes among nicotine-deprived smokers. Exp Clin Psychopharmacol 20:63–70

Audrain-McGovern J, Rodriguez D, Epstein LH, Cuevas J, Rodgers K, Wileyto EP (2009) Does delay discounting play an etiological role in smoking or is it a consequence of smoking? Drug Alcohol Depend 103:99–106

Axon RN, Bradford WD, Egan BM (2009) The role of individual time preferences in health behaviors among hypertensive adults: a pilot study. J Am Soc Hypertens 3:35–41

Baker F, Johnson MW, Bickel WK (2003) Delay discounting in current and never-before cigarette smokers: similarities and differences across commodity, sign, and magnitude. J Abnorm Psychol 112:382–392

Bari A, Robbins TW (2013) Inhibition and impulsivity: behavioral and neural basis of response control. Prog Neurobiol 108:44–79

Barkley RA, Edwards G, Laneri M, Fletcher K, Metevia L (2001) Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). J Abnorm Child Psychol 29(6):541–556

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7–15

Bickel WK, Green L, Vuchinich RE (1995) Behavioral economics (Editorial). J Exp Anal Behav 64:257–262

Bickel WK, Odum AL, Madden GJ (1999) Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. Psychopharmacology 146:447–454
Bickel WK, Wilson AG, Franck CT, Mueller ET, Jarmolowicz DP, Koffarnus MN, Fede SJ (2014) Using crowdsourcing to compare temporal, social temporal, and probability discounting among obese and non-obese individuals. Appetite 75:82–89
Bobova L, Finn PR, Rickert ME, Lucas J (2009) Disinhibitory psychopathology and delay discounting in alcohol dependence: personality and cognitive correlates. Exp Clin Psychopharmacol 17(1):51
Boettiger CA, Kelley EA, Mitchell JM, D'Esposito M, Fields HL (2009) Now or later? An fMRI study of the effects of endogenous opioid blockade on a decision-making network. Pharmacol Biochem Behav 93:291–299
Bradford WD (2010) The association between individual time preferences and health maintenance habits. Med Decis Mak 30:99–112
Bridge JA, Reynolds B, McBee-Strayer SM, Sheftall AH, Ackerman J, Stevens J et al (2015) Impulsive aggression, delay discounting, and adolescent suicide attempts: effects of current psychotropic medication use and family history of suicidal behavior. J Child Adolesc Psychopharmacol 25(2):114–123
Bulley A, Gullo MJ (2017) The influence of episodic foresight on delay discounting and demand for alcohol. Addict Behav 66:1–6
Cáceda R, Durand D, Cortes E, Prendes-Alvarez S, Moskovciak T, Harvey PD, Nemeroff CB (2014) Impulsive choice and psychological pain in acutely suicidal depressed patients. Psychosom Med 76(6):445–451
Celio MA, Mackillop J, Caswell AJ, Mastroleo NR, Kahler CW, Barnett NP, Colby SM, Operario D, Monti PM (2016) Interactive relationships between sex-related alcohol expectancies and delay discounting on risky sex. Alcohol Clin Exp Res 40
Cho SS, Ko JH, Pellecchia G, Van Eimeren T, Cilia R, Strafella AP (2010) Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level. Brain Stimul 3:170–176
Cho SS, Pellecchia G, Ko JH, Ray N, Obeso I, Houle S, Strafella AP (2012) Effect of continuous theta burst stimulation of the right dorsolateral prefrontal cortex on cerebral blood flow changes during decision making. Brain Stimul 5:116–123
Cho SS, Koshimori Y, Aminian K, Obeso I, Rusjan P, Lang AE, Daskalakis ZJ, Houle S, Strafella AP (2015) Investing in the future: stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. Neuropsychopharmacology 40:546–553
Coffey SF, Gudleski GD, Saladin ME, Brady KT (2003) Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. Exp Clin Psychopharmacol 11 (1):18
Copping LT, Campbell A, Muncer S (2014) Conceptualizing time preference: a life-history analysis. Evol Psychol 12:147470491401200
Daniel TO, Stanton CM, Epstein LH (2013) The future is now: reducing impulsivity and energy intake using episodic future thinking. Psychol Sci 24:2339–2342
Daugherty JR, Brase GL (2010) Taking time to be healthy: predicting health behaviors with delay discounting and time perspective. Personal Individ Differ 48(2):202–207
Davis C, Patte K, Curtis C, Reid C (2010) Immediate pleasures and future consequences. A neuropsychological study of binge eating and obesity. Appetite 54(1):208–213
de Wit H, Richards JB (2004) Dual determinants of drug use in humans: reward and impulsivity. Neb Symp Motiv 50:19–55
de Wit H, Enggasser JL, Richards JB (2002) Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. Neuropsychopharmacology 27:813–825
Decker JH, Figner B, Steinglass JE (2015) On weight and waiting: delay discounting in anorexia nervosa pretreatment and posttreatment. Biol Psychiatry 78(9):606–614
Del Giudice M, Gangestad SW, Kaplan HS (2015) Life history theory and evolutionary psychology. In: The handbook of evolutionary psychology. Wiley, Hoboken, pp 1–27

Demurie E, Roeyers H, Baeyens D, Sonuga-Barke E (2012) Temporal discounting of monetary rewards in children and adolescents with ADHD and autism spectrum disorders. Dev Sci 15 (6):791–800

Dombrovski AY, Szanto K, Siegle GJ, Wallace ML, Forman SD, Sahakian B et al (2011) Lethal forethought: delayed reward discounting differentiates high-and low-lethality suicide attempts in old age. Biol Psychiatry 70(2):138–144

Dougherty DM, Charles NE, Mathias CW, Ryan SR, Olvera RL, Liang Y, Acheson A (2014) Delay discounting differentiates pre-adolescents at high and low risk for substance use disorders based on family history. Drug Alcohol Depend 143:105–111

Eisenberg DTA, MacKillop J, Modi M, Beauchemin J, Dang D, Lisman SA, Lum JK, Wilson DS (2007) Examining impulsivity as an endophenotype using a behavioral approach: a DRD2 TaqI A and DRD4 48-bp VNTR association study. Behav Brain Funct 3

Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146:348–361

Eysenck SB, Eysenck HJ (1978) Impulsiveness and venturesomeness: their position in a dimensional system of personality description. Psychol Rep 43:1247–1255

Fernie G, Peeters M, Gullo MJ, Christiansen P, Cole JC, Sumnall H, Field M (2013) Multiple behavioural impulsivity tasks predict prospective alcohol involvement in adolescents. Addiction 108:1916–1923

Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, Fehr E, Weber EU (2010) Lateral prefrontal cortex and self-control in intertemporal choice. Nat Neurosci 13(5):538–539

Fillmore MT, Weafer J (2013) Behavioral inhibition and addiction. In: MacKillop J, de Wit H (eds) The Wiley-Blackwell handbook of addiction psychopharmacology. Wiley, Chichester, pp 135–164

Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK, Frank MJ (2013) Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. Biol Psychiatry 74 (2):130–136

Gray JC, Sanchez-Roige S, de Wit H, MacKillop J, Palmer AA (2019) Genomic basis of delayed reward discounting. Behav Process 162:157–161

Green L, Myerson J (2004) A discounting framework for choice with delayed and probabilistic rewards. Psychol Bull 130:769–792

Green L, Fry AF, Myerson J (1994) Discounting of delayed rewards: a life-span comparison. Psychol Sci 5:33–36

Griskevicius V, Tybur JM, Delton AW, Robertson TE (2011) The influence of mortality and socioeconomic status on risk and delayed rewards: a life history theory approach. J Pers Soc Psychol 100:1015–1026

Hart AB, de Wit H, Palmer AA (2013) Candidate gene studies of a promising intermediate phenotype: failure to replicate. Neuropsychopharmacology 38:802–816

Hecht D, Walsh V, Lavidor M (2013) Bi-frontal direct current stimulation affects delay discounting choices. Cogn Neurosci 4:7–11

Heerey EA, Matveeva TM, Gold JM (2011) Imagining the future: degraded representations of future rewards and events in schizophrenia. J Abnorm Psychol 120(2):483

Heerey EA, Robinson BM, McMahon RP, Gold JM (2007) Delay discounting in schizophrenia. Cogn Neuropsychiatry 12(3):213–221

Heil SH, Johnson MW, Higgins ST, Bickel WK (2006) Delay discounting in currently using and currently abstinent cocaine-dependent outpatients and non-drug-using matched controls. Addict Behav 31(7):1290–1294

Hofmeyr A, Ainslie G, Charlton R, Ross D (2010) The relationship between addiction and reward bundling: an experiment comparing smokers and non-smokers. Addiction 106:402–409

Hurst RM, Kepley HO, McCalla MK, Livermore MK (2011) Internal consistency and discriminant validity of a delay-discounting task with an adult self-reported ADHD sample. J Atten Disord 15 (5):412–422

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 167:748–751

Isen JD, Sparks JC, Iacono WG (2014) Predictive validity of delay discounting behavior in adolescence: a longitudinal twin study. Exp Clin Psychopharmacol 22:434–443
Jarmolowicz DP, Bickel WK, Carter AE, Franck CT, Mueller ET (2012) Using crowdsourcing to examine relations between delay and probability discounting. Behav Process 91:308–312
Johnson MW, Bickel WK, Baker F (2007) Moderate drug use and delay discounting: a comparison of heavy, light, and never smokers. Exp Clin Psychopharmacol 15(2):187
Johnson MW, Bruner NR (2012) The sexual discounting task: HIV risk behavior and the discounting of delayed sexual rewards in cocaine dependence. Drug Alcohol Depend 123:15–21
Jones J, Guest JL, Sullivan PS, Sales JM, Jenness S, Kramer MR (2018) The association between monetary and sexual delay discounting and risky sexual behavior in an online sample of men who have sex with men. AIDS Care 30:844–852
Kenny PJ (2011) Common cellular and molecular mechanisms in obesity and drug addiction. Nat Rev Neurosci 12(11):638–651
Kim-Spoon J, Lauharatanahirun N, Peviani K, Brieant A, Deater-Deckard K, Bickel WK, King-Casas B (2019) Longitudinal pathways linking family risk, neural risk processing, delay discounting, and adolescent substance use. J Child Psychol Psychiatry 60:655–664
Kirby KN, Guastello B (2001) Making choices in anticipation of similar future choices can increase self-control. J Exp Psychol Appl 7:154–164
Kirby KN, Maraković NN (1996) Delay-discounting probabilistic rewards: rates decrease as amounts increase. Psychon Bull Rev 3:100–104
Kirby KN, Petry NM (2004) Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction 99(4):461–471
Kirby KN, Petry NM, Bickel WK (1999) Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. J Exp Psychol Gen 128:78–87
Koffarnus MN, Bickel WK (2014) A 5-trial adjusting delay discounting task: accurate discount rates in less than one minute. Exp Clin Psychopharmacol
Laibson D (1997) Golden eggs and hyperbolic discounting. Q J Econ 112:443–478
Lawyer SR, Mahoney CT (2018) Delay discounting and probability discounting, but not response inhibition, are associated with sexual risk taking in adults. J Sex Res 55:863–870
Lee CA, Derefinko KJ, Milich R, Lynam DR, DeWall CN (2017) Longitudinal and reciprocal relations between delay discounting and crime. Pers Individ Dif 111:193–198
Lee AJ, DeBruine LM, Jones BC (2018) Individual-specific mortality is associated with how individuals evaluate future discounting decisions. Proc Biol Sci:285
Lejuez CW, Aklin WM, Zvolensky MJ, Pedulla CM (2003) Evaluation of the Balloon Analogue Risk Task (BART) as a predictor of adolescent real-world risk-taking behaviours. J Adolesc 26:475–479
Lempert KM, Steinglass JE, Pinto A, Kable JW, Simpson HB (2019) Can delay discounting deliver on the promise of RDoC? Psychol Med 49:190–199
Li JZ, Li S, Liu H (2011) How has the wenchuan earthquake influenced people's intertemporal choices? 1. J Appl Soc Psychol 41(11):2739–2752
Lovallo WR (2013) Early life adversity reduces stress reactivity and enhances impulsive behavior: implications for health behaviors. Int J Psychophysiol 90(1):8–16
Lowman C, Allen J, Stout RL (1996) Replication and extension of Marlatt's taxonomy of relapse precipitants: overview of procedures and results. The Relapse Research Group. Addiction 91 (Suppl):S51–S71
MacKillop J (2013) Integrating behavioral economics and behavioral genetics: delayed reward discounting as an endophenotype for addictive disorders. J Exp Anal Behav 99:14–31
MacKillop J, Anderson EJ, Castelda BA, Mattson RE, Donovick PJ (2006) Divergent validity of measures of cognitive distortions, impulsivity, and time perspective in pathological gambling. J Gambl Stud 22:339–354
MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, Munafò MR (2011) Delayed reward discounting and addictive behavior: a meta-analysis. Psychopharmacology 216:305–321
MacKillop J, Miller JD, Fortune E, Maples J, Lance CE, Campbell WK, Goodie AS (2014) Multidimensional examination of impulsivity in relation to disordered gambling. Exp Clin Psychopharmacol 22

MacKillop J, Celio MA, Mastroleo NR, Kahler CW, Operario D, Colby SM, Barnett NP, Monti PM (2015a) Behavioral economic decision making and alcohol-related sexual risk behavior. AIDS Behav 19:450–458

MacKillop J, Gray JC, Bidwell LC, Bickel WK, Sheffer CE, McGeary JE (2015b) Genetic influences on delay discounting in smokers: examination of a priori candidates and exploration of dopamine-related haplotypes. Psychopharmacology 232:3731–3739

MacKillop J, Weafer J, Gray JC, Oshri A, Palmer A, de Wit H (2016) The latent structure of impulsivity: impulsive choice, impulsive action, and impulsive personality traits. Psychopharmacology 233(18):3361–3370

Mackillop J, Gray JC, Weafer J, Sanchez-Roige S, Palmer AA (2019) Genetic influences on delayed reward discounting: a genome-wide prioritized subset approach. Exp Clin Psychopharmacol 27:29–37

Madden GJ, Petry NM, Badger GJ, Bickel WK (1997) Impulsive and self-control choices in opioid-dependent patients and non-drug-using control patients: drug and monetary rewards. Exp Clin Psychopharmacol 5(3):256

Madden GJ, Smith NG, Brewer AT, Pinkston JW, Johnson PS (2008) Steady-state assessment of impulsive choice in Lewis and Fischer 344 rats: between-condition delay manipulations. J Exp Anal Behav 90:333–344

Manwaring JL, Green L, Myerson J, Strube MJ, Wilfley DE (2011) Discounting of various types of rewards by women with and without binge eating disorder: evidence for general rather than specific differences. Psychol Rec 61(4):561–582

Mathias CW, Dougherty DM, James LM, Richard DM, Dawes MA, Acheson A, Hill-Kapturczak N (2011) Intolerance to delayed reward in girls with multiple suicide attempts. Suicide Life Threat Behav 41(3):277–286

Mazur JE (1987) An adjusting procedure for studying delayed reinforcement. In: Commons ML, Mazur JE, Nevin JA, Rachlin H (eds) The Effect of delay and of intervening events on reinforcement value: quantitative analyses of behavior, vol 5. Lawrence Erlbaum Associates Inc, Hillsdale, NJ, pp 55–73

Mazur JE, Logue AW (1978) Choice in a "self-control" paradigm: effects of a fading procedure. J Exp Anal Behav 30(1):11–17

Mendez IA, Simon NW, Hart N, Mitchell MR, Nation JR, Wellman PJ, Setlow B (2010) Self-administered cocaine causes long-lasting increases in impulsive choice in a delay discounting task. Behav Neurosci 124:470–477

Miller JD, Lynam DR (2013) Personality and addiction: a critical review of assessment approaches. In: MacKillop J, de Wit H (eds) The Wiley-Blackwell handbook of addiction psychopharmacology. Wiley, Chichester, pp 111–133

Mischel W (1958) Preference for delayed reinforcement: an experimental study of a cultural observation. J Abnorm Psychol 56:57–61

Mischel W (1974) Processes in delay of gratification. Adv Exp Soc Psychol 7:249–292

Mischel W, Shoda Y, Rodriguez MI (1989) Delay of gratification in children. Science 244:933–938

Mitchell JM, Fields HL, D'Esposito M, Boettiger CA (2005) Impulsive responding in alcoholics. Alcohol Clin Exp Res 29:2158–2169

Mitchell JM, Tavares VC, Fields HL, D'Esposito M, Boettiger CA (2007) Endogenous opioid blockade and impulsive responding in alcoholics and healthy controls. Neuropsychopharmacology 32:439–449

Mitchell MR, Weiss VG, Ouimet DJ, Fuchs RA, Morgan D, Setlow B (2014) Intake-dependent effects of cocaine self-administration on impulsive choice in a delay discounting task. Behav Neurosci 128:419–429

Mole TB, Irvine MA, Worbe Y, Collins P, Mitchell SP, Bolton S et al (2015) Impulsivity in disorders of food and drug misuse. Psychol Med 45(4):771–782

Murphy C, Mackillop J (2012) Living in the here and now: interrelationships between impulsivity, mindfulness, and alcohol misuse. Psychopharmacology 219:527–536

Odum AL (2011) Delay discounting: I'm a k, you're a k. J Exp Anal Behav 96:427–439

Odum AL, Madden GJ, Bickel WK (2002) Discounting of delayed health gains and losses by current, never- and ex-smokers of cigarettes. Nicotine Tob Res 4:295–303

Oshri A, Kogan SM, Kwon JA, Wickrama KAS, Vanderbroek L, Palmer AA, Mackillop J (2018) Impulsivity as a mechanism linking child abuse and neglect with substance use in adolescence and adulthood. Dev Psychopathol 30(2):417–435

Owens MM, Syan SK, Amlung M, Beach SRH, Sweet LH, MacKillop J (2019) Functional and structural neuroimaging studies of delayed reward discounting in addiction: a systematic review. Psychol Bull 145:141–164

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51:768–774

Perkins FN, Freeman KB (2018) Pharmacotherapies for decreasing maladaptive choice in drug addiction: targeting the behavior and the drug. Pharmacol Biochem Behav 164:40–49

Perry JL, Larson EB, German JP, Madden GJ, Carroll ME (2005) Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. Psychopharmacology 178:193–201

Petry NM (2001) Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. Psychopharmacology 154:243–250

Pulcu E, Zahn R, Elliott R (2013) The role of self-blaming moral emotions in major depression and their impact on social-economical decision making. Front Psychol 4:310

Pulcu E, Trotter PD, Thomas EJ, McFarquhar M, Juhász G, Sahakian BJ et al (2014) Temporal discounting in major depressive disorder. Psychol Med 44(9):1825–1834

Peviani KM, Kahn RE, Maciejewski D, Bickel WK, Deater-Deckard K, King-Casas B, Kim-Spoon J (2019) Intergenerational transmission of delay discounting: the mediating role of household chaos. J Adolesc 72:83–90

Pietras CJ, Cherek DR, Lane SD, Tcheremissine OV, Steinberg JL (2003) Effects of methylphenidate on impulsive choice in adult humans. Psychopharmacology 170:390–398

Pinto A, Steinglass JE, Greene AL, Weber EU, Simpson HB (2014) Capacity to delay reward differentiates obsessive-compulsive disorder and obsessive-compulsive personality disorder. Biol Psychiatry 75(8):653–659

Reimers S, Maylor EA, Stewart N, Chater N (2009) Associations between a one-shot delay discounting measure and age, income, education and real-world impulsive behavior. Pers Individ Dif 47:973–978

Reynolds B, Schiffbauer R (2004) Measuring state changes in human delay discounting: an experiential discounting task. Behav Process 67:343–356

Richards JB, Zhang L, Mitchell SH, de Wit H (1999) Delay or probability discounting in a model of impulsive behavior: effect of alcohol. J Exp Anal Behav 71:121–143

Ritschel F, King JA, Geisler D, Flohr L, Neidel F, Boehm I et al (2015) Temporal delay discounting in acutely ill and weight-recovered patients with anorexia nervosa. Psychol Med 45(6):1229–1239

Robinson ESJ, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, Dalley JW, Robbins TW (2008) Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology 33:1028–1037

Rung JM, Madden GJ (2018) Experimental reductions of delay discounting and impulsive choice: a systematic review and meta-analysis. J Exp Psychol Gen 147:1349–1381

Sanchez-Roige S, Fontanillas P, Elson SL, Pandit A, Schmidt E, Forster J et al (2017) Genome-wide association study of delay discounting in 23,217 adult research participants of European ancestry. bioRxiv, 146936

Sanchez-Roige S, Fontanillas P, Elson SL, Pandit A, Schmidt EM, Foerster JR, Abecasis GR, Gray JC, de Wit H, Davis LK, MacKillop J, Palmer AA, Palmer AA (2018) Genome-wide association study of delay discounting in 23,217 adult research participants of European ancestry. Nat Neurosci 21:16–18

Scheres A, Sumiya M, Thoeny AL (2010) Studying the relation between temporal reward discounting tasks used in populations with ADHD: a factor analysis. Int J Methods Psychiatr Res 19(3):167–176

Schmaal L, Goudriaan AE, Joos L, Dom G, Pattij T, van den Brink W, Veltman DJ (2014) Neural substrates of impulsive decision making modulated by modafinil in alcohol-dependent patients. Psychol Med 44:2787–2798

Schneider S, Peters J, Peth JM, Büchel C (2014) Parental inconsistency, impulsive choice and neural value representations in healthy adolescents. Transl Psychiatry 4:e382–e382

Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, Doya K (2008) Low-serotonin levels increase delayed reward discounting in humans. J Neurosci 28(17):4528–4532

Schweitzer JB, Sulzer-Azaroff B (1988) Self-control: teaching tolerance for delay in impulsive children. J Exp Anal Behav 50:173–186

Shafiei N, Gray M, Viau V, Floresco SB (2012) Acute stress induces selective alterations in cost/benefit decision-making. Neuropsychopharmacology 37:2194–2209

Sheffer CE, Mennemeier M, Landes RD, Bickel WK, Brackman S, Dornhoffer J, Kimbrell T, Brown G (2013) Neuromodulation of delay discounting, the reflection effect, and cigarette consumption. J Subst Abus Treat 45:206–214

Shen B, Yin Y, Wang J, Zhou X, McClure SM, Li J (2016) High-definition tDCS alters impulsivity in a baseline-dependent manner. Neuroimage 143:343–352

Shiels K, Hawk LW, Reynolds B, Mazzullo RJ, Rhodes JD, Pelham WE, Waxmonsky JG, Gangloff BP, Hawk LW Jr, Pelham WE Jr (2009) Effects of methylphenidate on discounting of delayed rewards in attention deficit/hyperactivity disorder. Exp Clin Psychopharmacol 17:291–301

Simmen-Janevska K, Forstmeier S, Krammer S, Maercker A (2015) Does trauma impair self-control? Differences in delaying gratification between former indentured child laborers and nontraumatized controls. Violence Vict 30:1068–1081

Sonuga-Barke EJS, Taylor E, Sembi S, Smith J (1992) Hyperactivity and delay aversion—I. The effect of delay on choice. J Child Psychol Psychiatry 33(2):387–398

Smits RR, Stein JS, Johnson PS, Odum AL, Madden GJ (2013) Test-retest reliability and construct validity of the Experiential Discounting Task. Exp Clin Psychopharmacol 21

Stein JS, Smits RR, Johnson PS, Liston KJ, Madden GJ (2013) Effects of reward bundling on male rats' preference for larger-later food rewards. J Exp Anal Behav 99:150–158

Stein JS, Wilson AG, Koffarnus MN, Daniel TO, Epstein LH, Bickel WK (2016) Unstuck in time: episodic future thinking reduces delay discounting and cigarette smoking. Psychopharmacology 233

Stein JS, Tegge AN, Turner JK, Bickel WK (2018) Episodic future thinking reduces delay discounting and cigarette demand: an investigation of the good-subject effect. J Behav Med 41:269–276

Steinglass JE, Figner B, Berkowitz S, Simpson HB, Weber EU, Walsh BT (2012) Increased capacity to delay reward in anorexia nervosa. J Int Neuropsychol Soc 18(4):773–780

Still GF (2006) Some abnormal psychical conditions in children: excerpts from three lectures. J Atten Disord 10(2):126–136

Stojek MMK, MacKillop J (2017) Relative reinforcing value of food and delayed reward discounting in obesity and disordered eating: a systematic review. Clin Psychol Rev 55:1–11

Sun H, Cocker PJ, Zeeb FD, Winstanley CA (2012) Chronic atomoxetine treatment during adolescence decreases impulsive choice, but not impulsive action, in adult rats and alters markers of synaptic plasticity in the orbitofrontal cortex. Psychopharmacology 219:285–301

Sweitzer MM, Halder I, Flory JD, Craig AE, Gianaros PJ, Ferrell RE, Manuck SB (2013) Polymorphic variation in the dopamine D4 receptor predicts delay discounting as a function of childhood socioeconomic status: evidence for differential susceptibility. Soc Cogn Affect Neurosci 8:499–508

Van Den Berk-Clark C, Myerson J, Green L, Grucza RA (2018) Past trauma and future choices: differences in discounting in low-income, urban African Americans. Psychol Med 48 (16):2702–2709

VanderBroek L, Acker J, Palmer AA, de Wit H, MacKillop J (2016) Interrelationships among parental family history of substance misuse, delay discounting, and personal substance use. Psychopharmacology 233(1):39–48

VanderBroek-Stice L, Stojek MK, Beach SRH, vanDellen MR, MacKillop J (2017) Multidimensional assessment of impulsivity in relation to obesity and food addiction. Appetite 112:59–68

Vuchinich RE, Simpson CA (1998) Hyperbolic temporal discounting in social drinkers and problem drinkers. Exp Clin Psychopharmacol 6(3):292

Weller RE, Avsar KB, Cox JE, Reid MA, White DM, Lahti AC (2014) Delay discounting and task performance consistency in patients with schizophrenia. Psychiatry Res 215(2):286–293

Whiteside SP, Lynam DR (2001) The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. Pers Individ Dif 30:669–689

Winstanley CA (2011) Themed issue: translational neuropharmacology-using appropriate animal models to guide clinical drug development. The utility of rat models of impulsivity in developing pharmacotherapies for impulse control disorders. Br J Pharmacol 164(4):1301–1321

Xia L, Gu R, Zhang D, Luo Y (2017) Anxious individuals are impulsive decision-makers in the delay discounting task: an ERP study. Front Behav Neurosci 11:5

Yu LQ, Lee S, Katchmar N, Satterthwaite TD, Kable JW, Wolf DH (2017) Steeper discounting of delayed rewards in schizophrenia but not first-degree relatives. Psychiatry Res 252:303–309

Reinforcer Pathology: Implications for Substance Abuse Intervention

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Abstract The rate at which individuals discount future rewards (i.e., discounting rate) is strongly associated with their propensity for substance abuse as well as myriad other negative health behaviors. An excessive preference for immediately available rewards suggests a shortened time horizon in which immediate rewards are overvalued and future, potentially negative consequences are undervalued. This review outlines Reinforcer Pathology Theory (i.e., the interaction between excessive preference for immediately available rewards and the overvaluation of a particular commodity that offers brief, intense reinforcement), its neurobiological/behavioral underpinnings, and its implications for treating substance use disorders. In doing so, the current review provides an overview of a variety of ways in which interventions have been used to manipulate aspects of reinforcer pathology in an individual, including narrative theory, framing manipulations, and neuromodulation (e.g., working memory training, TMS) which may serve as promising avenues for the modulation of the temporal window and/or valuation of reinforcers.

Keywords Addiction · Behavioral economic demand · Delay discounting · Narrative theory · Reinforcer pathology · Temporal window · Valuation of rewards

1 Introduction

Addiction is one of the leading public health challenges in the USA (Nutt et al. 2006; NIDA 2005) with an estimated annual cost of over $600 billion dollars (Volkow 2011). More than 20 million Americans meet diagnostic criteria for substance use disorders (SUDs) other than for tobacco (U.S. Department of Health and Human Services (HHS) 2016). Although existing substance abuse services are efficacious and replicable, considerable opportunities for improvement remain (Rösner et al. 2010). For example, only one in nine individuals with alcohol use disorder (AUD) benefits from treatment with medication, and brief psychotherapeutic interventions produce only small reductions in alcohol consumption (Foxcroft et al. 2016; Klimas et al. 2012). Perhaps this limited success is a result of treatments that were not designed specifically to modify any core feature of the disorder (e.g., Ahn and Wampold 2001; Bell et al. 2013). This lack of target specificity of psychotherapeutic treatments raises the question of how to develop a treatment that targets the core features of a disorder.

One process-driven answer to that question is the Experimental Medicine Approach developed by Claude Bernard in his classic text published in 1865, *An Introduction to the Study of Experimental Medicine* (Bernard 1957; Nielsen et al. 2018). The Experimental Medicine Approach consists of four steps (Bernard 1957; Nielsen et al. 2018). First, develop a hypothesis of a core process of the disorder.

Second, devise a way to measure that process. Third, ascertain if that process is observed in the disorder. Fourth, deploy an intervention that engages the disorder-related process and determine if those changes produce any concomitant changes in any other components of the disorder (e.g., clinically relevant behavioral outcome changes). If the intervention changes the targeted processes as well as some other component of the disorder in a therapeutically appropriate way, then the intervention could be used as a treatment or part of a treatment, and that intervention would be one targeting a specific feature of the disorder.

With respect to addiction, a hypothesis was developed, based on clinical observations and then confirmed by early research, that those suffering from this disorder focus on the short-term and display an immediacy bias (Bickel et al. 2017; Petry 2001). Following up on that hypothesis, delay discounting (also referred to as temporal discounting, intertemporal choice, or time preference) was employed as a sensitive measure of this bias with appropriate granularity. In short, delay discounting is the rate at which an individual devalues a reward as a function of its delay to receipt (see Box 1). While delay discounting is a universal phenomenon, an excessive preference for immediately available rewards (i.e., high rate of discounting) suggests a shortened time horizon in which immediately available rewards are overvalued and future, potentially negative consequences are undervalued. Delay discounting is particularly relevant to alcohol and substance abuse. Early empirical findings, subsequent research, reviews, and meta-analyses have demonstrated that the rate at which individuals discount future rewards is strongly associated with their propensity for substance abuse as well as myriad other negative health behaviors (Amlung et al. 2016a, b for meta-analyses; see MacKillop et al. 2011; Snider et al. 2018a). Thus, this prior work can be seen as mapping on to the first three steps of the Experimental Medicine Approach. The fourth step, target engagement, informed a new conceptual model of addiction, referred to as Reinforcer Pathology Theory. Below we first describe this model and then review the data showing the effects of target engagement.

Box 1 Discounting and Valuation

*Delay discounting (*e.g.*, temporal discounting, intertemporal choice, time preference)* reflects the devaluation of a reinforcer as a function of the delay to its receipt. *Discounting tasks* offer a choice between a smaller and larger reward with a conditional delay or level of uncertainty in its receipt (e.g., $50 now or $100 later; 100% chance of $50 now or 75% chance of $100 now). Monetary reinforcers are commonly used due to their universality and fungible nature, though other reinforcers including food, drugs, and sex have also been utilized.

(continued)

Box 1 (continued)

*Reinforcer valuation (*e.g.*, craving, purchase tasks, self-administration)* can be assessed using several well-validated measures. *Craving* for a commodity can be assessed through multiple methods, including the measurement of self-reported intention to and/or relief from using the commodity (Sayette et al. 2000). *Purchase tasks* can assess behavioral economic demand for a reinforcer by allowing an agent to make real or hypothetical purchases across trials involving a range of prices (Roma et al. 2016). During *self-administration tasks*, individuals have the opportunity to work for and consume single units of a preferred commodity (Bickel et al. 1990).

2 Reinforcer Pathology Theory

The concept of a reinforcer pathology is defined as the interaction between two important behavioral economic processes: (1) excessive preference for immediately available rewards and (2) the overvaluation of a particular commodity that offers brief, intense reinforcement (Bickel et al. 2011a, 2014). First, excessive preference for immediate rewards, or immediacy bias, is a process that may be measured by delay discounting. As mentioned above, the process of delay discounting is strongly associated with alcohol and substance use severity. For example, current cigarette smokers discounted future monetary rewards significantly more than never-smokers and ex-smokers (Bickel et al. 1999), heroin-dependent participants discounted the future significantly more than non-users (Kirby et al. 1999), and individuals with AUD discounted both future monetary and alcohol rewards significantly more than non-drinkers (Petry 2001). Second, overvaluation of a reward may be measured by an individual's demand, craving, or self-administration of that commodity (see Box 1). Again, decades of literature have demonstrated a relationship between high value for a rewarding substance and severity of its use. For example, high demand and craving for alcohol predicted alcohol abuse and AUD (MacKillop et al. 2010a; Skidmore et al. 2014). The interaction of these two processes (discounting and valuation) has been described by an initial and an expanded version of Reinforcer Pathology Theory – 1.0 and 2.0, respectively.

Reinforcer Pathology Theory 1.0 Reinforcer Pathology Theory 1.0 describes that delay discounting and valuation interact to synergistically predict severity of use. The concept of a reinforcer pathology may be illustrated as a 2×2 matrix (Fig. 1). That is, the individuals with the highest discounting rates and greatest valuation for their substance may be those at the greatest risk of SUD (cell *D*). In contrast, individuals with the lowest rates of delay discounting and very little valuation for substances of abuse are at the least risk for SUD (cell *A*). Individuals who fall in cells *B* and *C* demonstrate intermediate risk between the extremes of cells *A* and *D*. Perhaps these individuals overuse, but can retain a job and fulfill family obligations. We note that the delineation of these metrics into one of four cells is a simplified

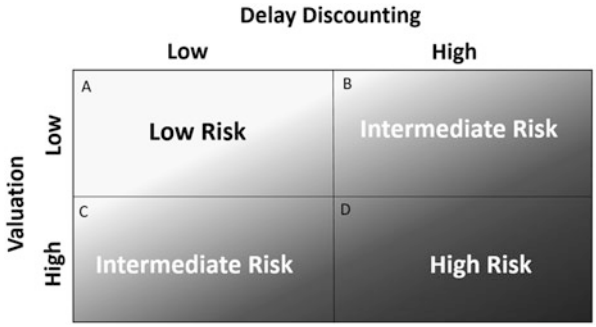

Fig. 1 Reinforcer pathology and substance abuse risk. Individuals in cell *A* (low discounting, low demand) and cell *D* (high discounting, high demand) display the lowest and highest risk for developing substance use disorders, respectively. Individuals with an intermediate risk for substance use disorders, cells *B* and *C*, may display a combination of high discounting/low demand or low discounting/high demand

heuristic. We have added shading to indicate that the probability of individuals at risk may fall along a continuum.

Reinforcer Pathology Theory 1.0 is supported empirically by studies examining how both delay discounting and valuation of a reward relate to severity of misuse. For example, monetary discounting and demand for alcohol predicted alcohol-related consequences, as measured by the Young Adult Alcohol Consequences Questionnaire, in college students (Lemley et al. 2016). That is, those with the greatest discounting rates and highest demand for alcohol demonstrated the greatest number of alcohol-related consequences. Reinforcer Pathology Theory 1.0 does not specify whether delay discounting, demand, and craving for alcohol are independent processes; however, they are all associated with AUD criteria in alcohol users and are intercorrelated with each other suggesting their overlap (MacKillop et al. 2010a).

The processes contributing to reinforcer pathology also map onto neurobiological mechanisms. The Competing Neurobehavioral Decision Systems (CNDS) theory describes two decision-making systems: (1) the impulsive decision system and (2) the executive decision system (Bechara and Damasio 2005; Bickel et al. 2007). The theory posits that the relative control between these two decision systems promotes either impulsive or self-controlled decision-making, respectively. For example, brain regions associated with the impulsive decision system including the ventral striatum, medial orbitofrontal cortex, and medial prefrontal cortex increased in activation when the subjective value of a reward increased and the delay to its receipt decreased (McClure et al. 2004). In contrast, the left dorsolateral prefrontal cortex (PFC), a structure of the executive decision system, promoted self-controlled decisions when presented with a delay discounting choice (Figner et al. 2010). Together, these examples illustrate that the processes driving reinforcer pathology can be derived from neuro-mechanistic underpinnings. Below we describe the neural circuits underlying these processes in greater detail. Importantly, the ability to identify functional phenotypes of severity of use may have a significant

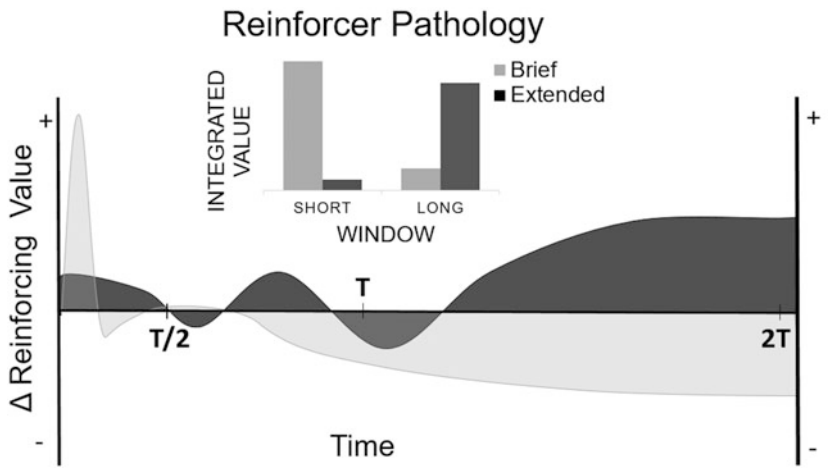

Fig. 2 The integrated values of two reinforcers over time (brief and extended reinforcers). The gray curve represents the subjective value of a brief reinforcer (e.g., drugs) at different time windows (*T*). The black curve represents the subjective value of an extended reinforcer (e.g., prosocial reinforcers) over the same windows. The areas under these curves represent integrated subjective value over the course of repeated choices for each reinforcer. Depending on the temporal window considered (*T/2*, *T*, or *2T*), the integrated value of the two reinforcers may reverse

impact on precision medicine. Understanding the risk phenotypes will help to both identify individuals at risk (Fig. 1; cell *D*) and develop effective treatment interventions. More recently, the concept of reinforcer pathology has evolved to interpret the interaction of delay discounting and valuation in greater detail.

Reinforcer Pathology Theory 2.0 Reinforcer Pathology Theory 2.0 describes how delay discounting and demand may interact by illustrating how individuals integrate valuation of rewards as a function of their temporal horizon (Fig. 2). Specifically, delay discounting functionally measures the temporal window (i.e., how far the individual can imagine into the future) over which reinforcer value can be integrated. That temporal window interacts with the value of different reinforcers depending on the length of the temporal horizon. Consider the following example: alcohol and other substances of abuse deliver brief, intense reinforcement with immediate and reliable effects. In contrast, prosocial reinforcers (e.g., employment, relationships) are lower intensity, inconsistent, and accrue their value over longer temporal windows. If an individual's temporal window is constricted (i.e., excessive delay discounting, Timepoint *T/2*), the summed relative value (area under the curves) is much greater for substance use than for prosocial reinforcers. This relative value translates, therefore, to overconsumption (i.e., overvaluation) and a lack of regard for delayed consequences – a reinforcer pathology. From this perspective, Reinforcer Pathology Theory 2.0 suggests the temporal window (i.e., an individual's rate of discounting) as the target for intervention. Reinforcer Pathology Theory 2.0 would predict that expansion of the temporal window should decrease overvaluation and

excessive demand of substances of abuse and conversely constriction of the temporal window would increase valuation. If these observations are supported, then this would be an example of how the Experimental Medicine Approach could identify potential interventions that target a disorder-specific process. Below we describe evidence for interventions that modulate the temporal window.

3 Lengthening and Shortening the Temporal Window

Reinforcer Pathology 2.0 suggests that interventions altering the temporal window should change valuation of substances of abuse. Hence, interventions that have been identified to modify discounting (Bickel et al. 2016a, b; Koffarnus et al. 2013; Rung and Madden 2018) have the potential of altering the valuation of substances. To date, only a small number of these interventions have investigated both discounting and valuation of reinforcers. In this section, we discuss a novel approach that has shown changes in both the temporal window and the valuation of substances, namely, narrative theory.

3.1 Narrative Theory

Human beings are storytellers by nature (Gregg 1991; Hermans 1993; McAdams 1988; McAdams et al. 2006). Over the last few decades, the field of psychotherapy has been greatly influenced by the increasing interest in studying narratives and discovering the power of telling a tale (e.g., Krippner et al. 2007; McLeod 1997; Meier 2012; Speedy 2008; White and Epston 1990). A novel framework of narrative theory (Bickel et al. 2017) that aims to harness humans' unique sensitivity to language and storytelling (Huth et al. 2016; Nummenmaa et al. 2014) has been utilized to study human behaviors and promote behavioral change. For example, narratives simulating future thinking (e.g., episodic future thinking (EFT)) are used to expand the temporal window of reward valuation, while narratives describing circumstances of insufficient resources (i.e., economic scarcity) are used to shorten the temporal window of reward valuation. Below, we discuss these examples in greater detail.

Episodic Future Thinking (EFT) EFT is a narrative intervention based on the new science of prospection that was first identified by Gilbert and Wilson in a Science publication in 2007. A growing body of evidence suggests that prospection is crucial for understanding human cognition, affect, motivation, and action (Seligman et al. 2013). Individuals with damaged frontal lobe areas, as well as individuals with addiction, show impaired prospective thinking (i.e., deficits in planning prospectively; Griffiths et al. 2012; Heffernan 2008; Kurczek et al. 2015). One systematic method to stimulate prospection is EFT, which is a narrative manipulation in which

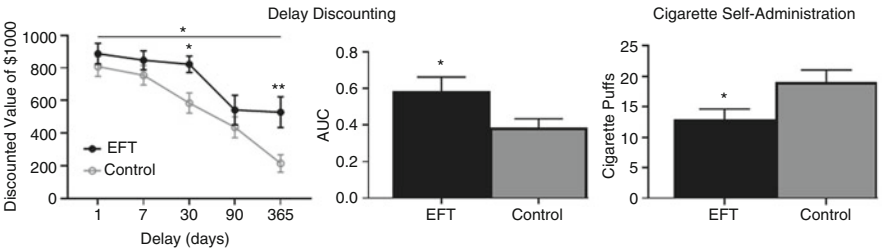

Fig. 3 Discounted value of $1,000 across increasing delays and corresponding area under the curve (AUC) values in episodic future thinking (EFT) and episodic recent thinking (ERT) participants (*left panels*). Also pictured is the number of cigarette puffs earned in the cigarette self-administration task (*right panel*) in EFT and ERT participants. Data replotted from Stein et al. (2016)

participants generate narratives describing their own potential future experiences. Previous studies indicated that EFT expands the temporal window of reward valuation (i.e., shift one's preference from immediate to long-term rewards) in individuals with AUD (Bulley and Gullo 2017; Snider et al. 2016), smokers (Chiou and Wu 2017; Stein et al. 2016, 2018), those who are overweight/obese, and controls (Daniel et al. 2013a, 2015; Kaplan et al. 2016; Peters and Büchel 2010). Consistent with reinforcer pathology, EFT not only expands the temporal window of reward valuation but also decreases behavioral economic demand for addictive substances, such as alcohol (Bulley and Gullo 2017; Snider et al. 2016), cigarettes (Stein et al. 2018), and food (Sze et al. 2017) in alcohol-dependent individuals, smokers, and overweight/obese individuals, respectively. Moreover, EFT reduced self-administration of rewards, such as highly palatable snacks among the obese (Daniel et al. 2013b, 2015; O'Neill et al. 2016) and cigarettes among smokers (e.g., Stein et al. 2016). For example, in a study by Stein et al. (2016), 42 participants were randomly assigned to the EFT or the episodic recent thinking groups (ERT; a commonly used control for the effects of prospection in EFT in which participants imagine real-life past events; Daniel et al. 2015; Lin and Epstein 2014). The findings of the study indicated significantly lower rates of discounting and self-administration of cigarette puffs (with a medium effect size) among participants in the EFT group compared to the ERT group (Fig. 3). Similarly, other narratives that lengthen the temporal window such as those describing a long-term romantic relationship increased preference for larger delayed rewards and decreased craving for cigarettes among cigarette smokers (Athamneh et al. 2019).

Economic Scarcity Economic scarcity is a narrative manipulation that describes situations of insufficient resources. Research and interest in investigating the effect of economic scarcity on decision-making have been increasing (Shah et al. 2012). Previous studies indicated that economic scarcity narratives (e.g., job loss and negative income shock) shorten the temporal window (Bickel et al. 2016c; Haushofer et al. 2013; Sze et al. 2017). Consistent with Reinforcer Pathology Theory 2.0, scarcity narratives shorten the temporal window and increase demand for unhealthy

food among overweight/obese individuals (Mellis et al. 2018; Sze et al. 2017). Similarly, other narratives that shorten the temporal window such as those describing a short-term sexual relationship increased preference for smaller immediate rewards and increased valuation of cigarettes among cigarette smokers (Athamneh et al. 2019). Moreover, reading a narrative describing a natural disaster (i.e., a hurricane) shortened the temporal window, increased demand for highly palatable snack foods, and increased total consumption of these snacks among obese individuals (Snider et al. 2019).

3.2 Other Interventions Manipulating the Temporal Window

In this section, we highlight some other interventions that have manipulated the temporal window, but that have not necessarily altered valuation mainly because valuation was not assessed. As a caveat, the following will not be an exhaustive discussion of these various manipulations, as several recent reviews have provided an excellent discussion (Koffarnus et al. 2013; Rung and Madden 2018) and readers are encouraged to consult these reviews for more details. Rather, we will highlight some of the promising approaches that may operate similarly to those interventions that have influenced both delay discounting and valuation measures and therefore directly manipulate the temporal window.

3.2.1 Lengthening the Temporal Window

Outcome Framing Several approaches have manipulated the way in which outcomes are framed to participants. In typical discounting tasks, two options are presented: an amount of money available now (e.g., $500 now) and an amount of money available after some delay (e.g., $1,000 in 1 year). Presenting options in this way *implicitly* suggests that if the immediate option is chosen, then any (larger) later amount of money is forgone. The converse is also true such that if the latter option is chosen, then any (smaller) immediate amount is forgone. In one type of framing manipulation, the money forgone is *explicitly* stated in each trial. When the explicit-zero manipulation is applied, the two discounting options become an amount of money available now and no money later (e.g., $500 now and $0 in 1 year) and no money now and an amount of money after some delay (e.g., $0 now and $1,000 in 1 year).

Several studies have investigated whether explicitly framing outcomes reduces discounting rates (Koffarnus and Bickel 2014; Magen et al. 2008; Naudé et al. 2018; Radu et al. 2011; Wu and He 2012). Overall, these studies reported reductions in discounting after exposure to the explicit-zero manipulation, and as noted in the meta-analysis by Rung and Madden (2018), this manipulation resulted in significant decreases in impulsive choice (cf. Naudé et al. 2018).

A number of explanations have been proposed for why the explicit-zero manipulation results in decreased impulsive choice. Most relevant to Reinforcer Pathology Theory 2.0, Radu et al. (2011) propose that this intervention is acting upon the temporal window to shift focus toward more distal outcomes. By including "$0 in *X* delay" in the immediate option, attention is shifted away from the sooner option, and relatively more attention is allocated toward the larger monetary amount associated with the delayed alternative.

Delay Framing As depicted in the aforementioned examples, the delays associated with the outcomes are usually framed in terms of days, weeks, and years. Another way in which preference toward delayed outcomes has been manipulated is by changing the way delays are presented. Presenting options in terms of days, weeks, and years is considered *delay framing*. Alternatively, presenting options in terms of specific, concrete dates is considered *date framing*. For example, instead of presenting the larger, later option as "$1000 in 1 year," the option is framed as "$1000 on [actual date one year from today]."

A number of studies have evaluated how date framing affects discounting (DeHart and Odum 2015; Dshemuchadse et al. 2013; Klapproth 2012; Leboeuf 2006; cf. Naudé et al. 2018; Read et al. 2005). The fact that all of the aforementioned studies found that date framing reduced discounting is especially impressive given that these studies have recruited a diverse population including college students, adults, and substance users, as well as using a variety of different discounting tasks and measured outcomes. In a recent meta-analysis, Rung and Madden (2018) found framing delays as dates significantly reduced impulsive choice.

Several explanations have been proposed as to why date framing consistently reduces discounting (Rung and Madden 2018), including shifting attention toward the monetary amounts, rather than the delay, interfering with heuristics, and increasing the objective evaluation of the delay (i.e., a specific date may be perceived as more concrete). One explanation, consistent with *Reinforcer Pathology Theory 2.0*, could be that such manipulations are acting upon the temporal window. Two pieces of evidence may support this claim. First, as noted by Rung and Madden (2018), Klapproth (2012) found that substance users' discount rates after the date manipulation did not significantly differ from those of healthy controls. Expanding the temporal window by presenting the discounting task with dates instead of delays led to the absence of significant difference in discounting rates of substance users when compared to healthy controls. Second, Naudé et al. (2018) observed a rate-dependent effect such that those with higher initial discount rates reduced their discounting after the date manipulation; however, the date manipulation did not further reduce discount rates among those with already low initial discount rates. In addition, the date manipulation did not differentially affect participants with different smoking status (i.e., never, ex-, current smoker), although this may be due to individuals' initial discount rate explaining variance that would otherwise be attributed to differential smoking status.

Working Memory Training One potential intervention for reducing impulsive choice is through improving working memory (Brooks et al. 2017; Wesley and Bickel 2014). Working memory involves the central executive system which is important for self-regulation, decision-making, and problem solving (Barkley 2001; Barrett et al. 2004; Finn 2002). For example, in a study by Bickel et al. (2011c), participants completed several tasks related to working memory, such as auditory and visual recall. Participants who were exposed to this training showed decreases in discounting by approximately 50%. In a recent study, Felton et al. (2019) found that improvements in working memory, but not working memory training directly, significantly predicted decreases in discount rate. In addition, working memory training has been shown to improve processes that modulate delay discounting (e.g., EFT; Snider et al. 2018b). More research is needed, however, as this effect has not been consistently observed and may be due to a variety of reasons such as the specific impulsivity task used, the working memory training protocol implemented, or the way these results have been analyzed (Rass et al. 2015; Wanmaker et al. 2018). Nonetheless, improvements in working memory may be, to some extent, operating on the temporal window.

Transcranial Magnetic Stimulation (TMS) Transcranial magnetic stimulation, whereby cortical excitability is increased or decreased via electrical currents, has shown initial promise in modulating temporally related decision-making (Cho et al. 2015; Figner et al. 2010; Sheffer et al. 2013, 2018). For example, several studies have shown that application of TMS to the left dorsolateral prefrontal cortex (DLPFC; Sheffer et al. 2013, 2018) and medial prefrontal cortex (Cho et al. 2015) decreased discounting of monetary gains. Though Sheffer et al. (2013) did not find that an acute session of TMS affected subsequent consumption of cigarettes, a more recent longitudinal application (8 sessions) of TMS decreased the risk of relapse in abstinent smokers (Sheffer et al. 2018).

3.2.2 Shortening the Temporal Window

Transcranial Magnetic Stimulation (TMS) TMS has been shown to lengthen the temporal window by virtue of decreased discount rates and to shorten the temporal window. In one application (Figner et al. 2010), TMS applied to the left dlPFC resulted in greater preference for immediate rewards over-delayed rewards. Together, these studies suggest that TMS may alter the temporal window in two opposite directions. However, concurrent fMRI scanning after TMS application is necessary to determine whether a particular TMS procedure increases or decreases brain activity.

3.3 Other Interventions Changing Valuation

Several manipulations have been applied to changing valuation of substances, as measured via behavioral economic demand and cravings. In line with Reinforcer Pathology Theory 2.0, those interventions that alter the temporal window should also alter valuation for substances. Heretofore, we have discussed interventions targeting the temporal window, some of which have also shown changes in valuation. In contrast, we now discuss two primary manipulations that have targeted valuation, but that have not necessarily measured changes in discounting. An important note is that, consistent with Reinforcer Pathology Theory 2.0, changes in valuation do not necessarily have to result in changes in discounting. As few studies have examined changes in the temporal window concurrently with interventions targeted at changing valuation, more research is needed in this area to determine under what conditions a symmetrical effect is observed.

External Contingencies in the Alcohol Purchase Task Although relatively fewer studies have examined potential interventions within the area of behavioral economic demand, several manipulations may have implications for altering the temporal window. In recent years, behavioral economic demand has most frequently been evaluated using a simulated or hypothetical purchase task. Purchase tasks provide a brief instruction set specifying assumptions (e.g., imagine a typical situation in which you normally drink alcohol/smoke cigarettes; imagine you have the same income and savings), and respondents indicate how much of a substance (e.g., alcoholic drinks, cigarettes) they would purchase and consume at a range of prices per unit of substance (e.g., price per drink, price per cigarette; for reviews see Kaplan et al. (2018) and MacKillop (2016)).

A number of manipulations have modified the instruction set to include additional external contingencies. Most notably has been the use of next-day responsibilities (Gentile et al. 2012; Gilbert et al. 2014; Skidmore and Murphy 2011) and driving after drinking (Teeters and Murphy 2015). Skidmore and Murphy (2011) evaluated how demand changed when two next-day responsibilities, including a class and an exam in a sample of students, were introduced. The researchers found that demand was highest under the control condition (no next-day responsibilities), followed by a next-day class, followed by a next-day test. In a similar experiment, Teeters and Murphy (2015) evaluated changes in demand in a situation where participants were told to imagine they would be driving home in the evening after drinking at a bar. Participants showed reduced demand under this condition compared to a control condition with no external contingencies. Taken together, these manipulations may be indicative of operating on the temporal window, whereby imagining consequences in the future (whether that is at the end of the night or the next day) altered valuation by way of reducing demand for the target substance.

Cues Another method in which valuation has been changed is by the use of cues. Cues have been shown to reliably elicit cravings, which in turn results in increased self-administration in the laboratory (Perkins 2009; Tiffany and Conklin 2000), and

from a behavioral economic perspective cravings may be related to in-the-moment valuation of a substance. To date, cue exposure has been shown to increase cravings and demand valuation for cigarettes (Acker and MacKillop 2013; MacKillop et al. 2012), alcohol (MacKillop et al. 2010b), and cannabis (Metrik et al. 2016). Michael, Amlung, and MacKillop (2014) found that alcohol-related cues increased craving and some aspects of valuation related to alcohol, but that these cues did not affect discounting rate. On the other hand, Metrik et al. (2016) found that cannabis-related cues increased craving and valuation measures for cannabis, as well as increased the attentional bias toward cannabis-related stimuli, which could provide some evidence suggesting cues shortening the temporal window. Up until this point, we have broadly discussed Reinforcer Pathology Theory 2.0 in the context of behavioral interventions. In accordance with the Experimental Medicine Approach, once the target engagement demonstrates effects on aspects of the disorder, examination of the associated neuroscience becomes an important avenue for investigation.

4 Neural Circuits Underlying Time, Addiction, and Reinforcer Pathology

Healthy and non-addictive decision-making, as viewed within Reinforcer Pathology Theory 2.0, results from neural systems that are in balance. As discussed earlier, the CNDS theory posits that functional behavior results from a balance between impulsive reward system and executive system. The impulsive reward system is checked and balanced by the calculated, executive system (Bickel et al. 2007). The executive system consists of regions of the prefrontal and parietal cortices and regulates our executive functions such as attention, working memory, decision-making, planning, and behavioral inhibition (Bettcher et al. 2016). When faced with rewarding stimuli in our environment (e.g., alcohol, drugs, high-fat foods) that activate the impulsive system, consisting of limbic and paralimbic brain structures (e.g., midbrain, amygdala, posterior hippocampus, habenular commissure, striatum, insula, nucleus accumbens), the executive system ensures that control is maintained during consumption of these stimuli.

Addictive decision-making is marked by an overvaluation of immediate rewards and an overactivation of the impulsive system along with a devaluation of future rewards and an underactivation of the executive system (Bickel et al. 2014). As discussed previously, individuals with SUDs devalue the future, preferring smaller, immediate rewards over larger, long-term rewards. Short-term reinforcers, like alcohol and drugs, are powerful because they operate within short temporal windows. On the other hand, prosocial reinforcers such as family or employment have little value as these reinforcers tend to be rewarding within long temporal windows. Within this framework, we see that temporal organization may be altered in individuals with SUD. Indeed, individuals with SUDs show impairments in many types of memory including working memory, episodic memory (a form of long-term

memory for autobiographical events), prospective memory, as well as other areas of cognitive functioning (Domínguez-Salas et al. 2016; Gould 2010). These memory systems give us an organized timeline of events in which we can frame our experience. We remember when we did something, how long ago it occurred, and when we need to do something in the future. That is, the brain allows us to frame our conscious experience within distinct temporal windows (i.e., short versus long).

The delay discounting paradigm as a temporal window evaluator is sensitive to many maladaptive health behaviors including addiction, which make it an excellent behavioral marker to investigate brain mechanisms underlying addiction and recovery processes. Functional magnetic resonance imaging studies have shown that during delay discounting paradigms, when choosing the immediate over delayed reward, dopaminergically innervated areas of the impulsive system, including the ventral striatum, medial orbitofrontal cortex, and medial prefrontal cortex, are primarily activated (McClure et al. 2004, 2007). Areas of the executive system, on the other hand, including the dorso- and ventrolateral prefrontal cortex, the lateral orbitofrontal cortex, and the intraparietal cortex, show a greater level of relative activation (compared to the impulsive system) when choosing delayed over immediate rewards (McClure et al. 2004, 2007). In healthy individuals, greater discounting is associated with decreased activation of a frontoparietal-striatal network and a heightened activation of a temporal lobe network (Elton et al. 2017). Greater discounting is also associated with decreased prefrontal volume, leading to decreased executive decision system regulation, and heightened striatal and parahippocampal/hippocampal volume, leading to increased impulsive decision system regulation (Owens et al. 2017; Suckling and Nestor 2017; Tschernegg et al. 2015; Yu 2012). In addition, individuals with SUDs show altered functional connectivity between these networks, with greater alterations associated with greater discounting, greater levels of drug-related harm, and increased rates of drug relapse (Clewett et al. 2014; Contreras-Rodríguez et al. 2015; Yu 2012). Clearly, impulsive and addictive behaviors are associated with disordered brain structure, function, and connectivity in both impulsive and executive systems.

In order for recovery to occur, behaviors need to shift away from impulsive and unhealthy actions to planned and contemplative healthy decisions. Mechanistically speaking, the executive system needs to become fully functional and homeostatic balance needs to be restored between the impulsive and executive systems. As discussed above, researchers are focusing on developing behavioral and other interventional strategies to decrease impulsivity and possibly help improve recovery outcomes. In order to provide a mechanism for how decreasing delay discounting may serve as a therapeutic target for individuals with SUDs, we will need to understand the neural systems involved in delay discounting and how the brain modulates shifts in delay discounting during and/or after exposure to an intervention. A few recent studies have begun exploring these areas of research.

As discussed above, EFT, often referred to as mental time travel or prospective thinking, serves as a successful intervention to shift choices away from immediate and toward delayed rewards. A pivotal study by Peters and Büchel (2010) examined the neural mechanisms underlying the effect of EFT on delay discounting using

functional magnetic resonance imaging. The authors found that valuation signals in the anterior cingulate cortex (ACC) and functional coupling or co-activation between the ACC, the hippocampus, and the amygdala supported the shift toward decision-making that favored long-term, patient choices (Peters and Büchel 2010). A similar study showed that activation in the medial rostral prefrontal cortex predicted future-oriented choices and that this effect was also associated with functional connectivity between the medial rostral prefrontal cortex and the hippocampus (Benoit et al. 2011). These findings suggest that the prefrontal cortex may be using information from the amygdala and hippocampus to guide healthy decision-making.

A recent study showed that remembering positive autobiographical memories before delay discounting reduced subsequent delay discounting (Lempert et al. 2017). The authors suggest that the neural mechanism underlying this positive memory retrieval reduction in delay discounting is an increase in activity in the striatum and temporoparietal junction, which occurs during the process of memory retrieval (Lempert et al. 2017). In addition, individuals who showed the largest decreases in impulsivity showed the greatest levels of similarity in ventromedial prefrontal cortex activation during memory recall and intertemporal choice (Lempert et al. 2017).

Working memory training has also yielded reduced discounting rates in stimulant addicts (Bickel et al. 2011c). To determine the unique brain regions of plausible causality between working memory and delay discounting, Wesley and Bickel (2014) performed a matched activation likelihood estimation meta-analysis. The study findings revealed that a region of the left lateral prefrontal cortex is involved in both working memory and delay discounting (Wesley and Bickel 2014), which indicates that this region may be a key target for therapeutic interventions.

Beyond behavioral interventions, both pharmacological and non-invasive brain stimulation interventions have been shown to alter rates of delay discounting. Modafinil, an atypical dopamine reuptake inhibitor typically used for narcolepsy and sleep-wake disorders, was administered to alcohol-dependent patients. Modafinil decreased delay discounting, and this effect was accompanied by increased activation in frontoparietal regions, reduced activation in the ventromedial prefrontal cortex, and increased functional connectivity between the superior frontal gyrus and ventral striatum (Schmaal et al. 2014). TMS, a non-invasive procedure currently used to treat depression and other psychiatric disorders (Brunoni et al. 2019), has also been used as an acute intervention to decrease delay discounting. This technique uses pulses of electrical currents applied to the cortical surface to entrain neuronal firing beneath the electrode sites to particular frequencies, increasing or decreasing the activity of neuronal networks. A review examining non-invasive brain stimulation procedures, cognitive functioning, and impulsivity identified the dorsolateral prefrontal cortex as an important therapeutic target to alter delay discounting (Brevet-Aeby et al. 2016), with high-frequency (10 Hz) repetitive TMS (rTMS) being an effective protocol for decreasing delay discounting (Cho et al. 2015). More recently, a study in smokers showed that eight sessions of high-frequency rTMS of the left DLPFC in combination with smoking cessation

education materials decreased delay discounting, increased abstinence, reduced risk of relapse, and increased study engagement (Sheffer et al. 2018).

In addition, new work from our lab shows that demand, the other behavioral economic component of reinforcer pathology, recruits similar brain regions to delay discounting (Deshpande et al. 2019). Namely, both tasks engaged the superior/middle frontal cortex and superior/inferior parietal lobes, areas of the executive system (Deshpande et al. 2019). In a real-world cannabis purchasing task, the decision to purchase cannabis was associated with activation of the dorsal striatum, frontoparietal and posterior parietal regions, anterior and posterior cingulate cortex, anterior insula, DLPFC, and middle and superior temporal gyri, again regions involved in both the impulsive and executive systems (Bedi et al. 2015). More work is warranted to investigate the neural substrates underlying changes in demand, though we hypothesize that these may be similar therapeutic targets to those shown to underlie changes in delay discounting.

As a final note, imaging studies have shed some light on brain biomarkers in both the impulsive and executive systems that may predict successful abstinence and treatment response. For example, in alcohol-dependent patients, larger frontal and parietal cortices predict longer time to any alcohol use and heavy drinking relapse (Rando et al. 2011). In addition, methamphetamine users who remained abstinent compared to those who relapsed 1 year after study completion showed decreased activity in the inferior frontal gyrus (IFG) and striatum during reinforcement learning, but greater activity in the striatum, insula, IFG, and ACC during response feedback (Stewart et al. 2014). Previous research has also shown that the longer the period of abstinence, the more the brain recovers from addiction-related brain changes. Specifically, dopamine transporters in the striatum, which are a marker of dopamine terminals, significantly increased from a period of less than 6 months of abstinence to between 12 and 17 months of abstinence (Volkow et al. 2001).

Collectively, these studies suggest that interventions targeting a range of brain regions in either the impulsive or executive systems may be instrumental in shifting the temporal window to favor long-term, goal-oriented choices. Altering decision-making in individuals with SUDs to favor future outcomes over immediate rewards will most likely require distinct changes not only in prefrontal cortical networks that underlie executive functioning and basal ganglia circuits that underlie reward and motivation, but other regions that support these two key systems such as the hippocampus (memory), amygdala (emotion), and hypothalamus (stress).

5 Considerations for Intervention Development

As demonstrated above, substantial evidence exists to support the malleability of delay discounting and valuation, two key processes of Reinforcer Pathology Theory 2.0. Some manipulations may also intervene on addiction-common neural pathways, therefore providing a mechanism for addiction-related behavioral change. To date, however, important questions remain regarding both the permanency and

generalizability of interventions that target the temporal window. Before interventions on delay discounting or valuation, apart from or in tandem with other target behaviors (e.g., substance use) can be widely implemented, the following gaps in knowledge must be addressed.

First, despite the evidence that the temporal window can be changed, long-term follow-ups have not been conducted to establish the permanency of experimentally caused changes. Whereas some interventions may not be expected to produce lasting changes on the temporal window (e.g., date/delay framing or explicit-zero manipulation), more intensive interventions may create such a change. Interventions on delay discounting aimed at expanding the temporal window such as working memory training (Bickel et al. 2011c), financial education (DeHart et al. 2016; Lahav et al. 2015) or TMS (Cho et al. 2015) may create lasting, positive behavioral changes. Unfortunately, long-term follow-ups have yet to be conducted even when promising expansions of the temporal window have been established. In addition, the parameters of effective interventions including dose magnitude and treatment length are unknown. For example, if EFT can produce lasting changes in delay discounting, how often and for how long EFT must be administered and how often the individual must create new cues before they habituate remains unknown.

In regard to delay discounting specifically, while most interventions target monetary discounting, their effects on the discounting of other outcomes (e.g., food, alcohol) are less established. Some research suggests that delay discounting is a single, unitary trait-like process meaning that delay discounting is consistent across time (Kirby 2009) and between outcomes (Bickel et al. 2011b; Friedel et al. 2014). If this is true, then an intervention that changes monetary discounting should also change the discounting of other commodities. However, conflicting evidence also suggests that delay discounting can be domain specific (Jimura et al. 2011; Lawyer and Schoepflin 2013) meaning that how an individual discounts one outcome is not necessarily related to how they discount other outcomes. Consistent with Reinforcer Pathology Theory 2.0, an individual who steeply discounts one outcome likely discounts most outcomes steeply, reflecting constrained variability of the temporal window. Therefore, in these individuals, an intervention that extends the temporal window could result in a decrease in delay discounting across multiple domains. However, the predictions of Reinforcer Pathology Theory 2.0 for individuals who do not typically discount steeply are less clear. In this instance, interventions that reduce delay discounting may be domain specific, reflecting variability of the temporal window.

Perhaps the most important question regarding interventions that expand the temporal window is if temporary or permanent changes result in lasting improvements in related maladaptive behaviors such as substance use or overeating outside of laboratory settings. For example, due to the strong relationship between delay discounting and cigarette smoking, an intervention that directly targets delay discounting could, in turn, result in a reduction in cigarette smoking. In another example, O'Neill et al. (2016) found that EFT did reduce short-term out-of-lab calorie intake but delay discounting as the mechanism of EFT change was not assessed and a long-term follow-up was not conducted. To date, no study has

addressed these limitations. This gap presents a significant shortcoming in the scientific literature as the utility of delay discounting as a focus of intervention depends on its ability to produce meaningful behavioral changes and quality of life improvements beyond the laboratory. Furthermore, because of the wide range of behaviors that are related to delay discounting (Snider et al. 2018a), a reduction in delay discounting may not only improve the maladaptive target behavior but may improve overall functioning in a variety of domains (e.g., eating, exercise, finances). Such a finding would further establish delay discounting as a key behavioral phenotype and target of intervention.

6 Conclusion

Here we outlined Reinforcer Pathology Theory 2.0, its neurobiological/behavioral underpinnings, and its implications for treating SUDs. For decades, the development of effective remedies for addictions and other psychiatric disorders has been hampered by the lack of specific treatable targets. Recently, efforts have been made to remedy this by searching for precise, heritable mechanisms that undergird multiple disorders (Insel 2014). By utilizing the Experimental Medicine Approach, the temporal window of valuation, as measured by delay discounting, has emerged as one such mechanism, and its integration with reinforcer valuation into the theory of reinforcer pathology allows for an experimental framework through which to develop novel interventions. We have provided an overview of a variety of ways in which interventions have been used to manipulate aspects of Reinforcer Pathology Theory, including narrative theory, framing manipulations, and neuromodulation (e.g., working memory training, TMS). These manipulations appear to be promising avenues for the modulation of the temporal window and/or valuation of reinforcers among those individuals who demonstrate a reinforcer pathology. Importantly, this body of research demonstrates that temporal discounting is a determinant of the valuation of these reinforcers. This growing body of evidence is currently being translated to real-world settings, and if empirical findings continue to support the Reinforcer Pathology Theory, then the outcomes of many individuals suffering from substance use and obesity disorders may be improved.

References

Acker J, MacKillop J (2013) Behavioral economic analysis of cue-elicited craving for tobacco: a virtual reality study. Nicotine Tob Res 15(8):1409–1416

Ahn H-N, Wampold BE (2001) Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. J Couns Psychol 48(3):251–257

Amlung M, MacKillop J (2014) Understanding the effects of stress and alcohol cues on motivation for alcohol via behavioral economics. Alcohol Clin Exp Res 38(6):1780–1789

Amlung M, Petker T, Jackson J, Balodis I, MacKillop J (2016a) Steep discounting of delayed monetary and food rewards in obesity: a meta-analysis. Psychol Med 46(11):2423–2434
Amlung M, Vedelago L, Acker J, Balodis I, MacKillop J (2016b) Steep delay discounting and addictive behavior: a meta-analysis of continuous associations. Addiction 112(1):51–62. https://doi.org/10.1111/add.13535
Athamneh LN, Stein JS, Bickel WK (2019) Narrative theory III: evolutionary narratives addressing mating motives change discounting and tobacco valuation. Exp Clin Psychopharmacol. https://doi.org/10.1037/pha0000315
Barkley RA (2001) The executive functions and self-regulation: an evolutionary neuropsychological perspective. Neuropsychol Rev 11(1):1–29
Barrett LF, Tugade MM, Engle RW (2004) Individual differences in working memory capacity and dual-process theories of the mind. Psychol Bull 130(4):553
Bechara A, Damasio AR (2005) The somatic marker hypothesis: a neural theory of economic decision. Games Econ Behav 52(2):336–372
Bedi G, Lindquist MA, Haney M (2015) An fMRI-based neural signature of decisions to smoke cannabis. Neuropsychopharmacology 40(12):2657–2665
Bell EC, Marcus DK, Goodlad JK (2013) Are the parts as good as the whole? A meta-analysis of component treatment studies. J Consult Clin Psychol 81(4):722–736
Benoit RG, Gilbert SJ, Burgess PW (2011) A neural mechanism mediating the impact of episodic prospection on farsighted decisions. J Neurosci 31(18):6771–6779
Bernard C (1957) An introduction to the study of experimental medicine. Trans. from the French by H.C. Green. Dover Publications, New York
Bettcher BM, Mungas D, Patel N, Elofson J, Dutt S, Wynn M et al (2016) Neuroanatomical substrates of executive functions: beyond prefrontal structures. Neuropsychologia 85:100–109
Bickel WK, DeGrandpre RJ, Higgins ST, Hughes JR (1990) Behavioral economics of drug self-administration. I. Functional equivalence of response requirement and drug dose. Life Sci 47 (17):1501–1510
Bickel WK, Odum AL, Madden GJ (1999) Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. Psychopharmacology 146(4):447–454
Bickel WK, Miller ML, Yi R, Kowal BP, Lindquist DM, Pitcock JA (2007) Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. Drug Alcohol Depend 90(Suppl 1):S85–S91
Bickel WK, Jarmolowicz DP, Mueller ET, Gatchalian KM (2011a) The behavioral economics and neuroeconomics of reinforcer pathologies: implications for etiology and treatment of addiction. Curr Psychiatry Rep 13(5):406–415
Bickel WK, Landes RD, Christensen DR, Jackson L, Jones BA, Kurth-Nelson Z, Redish AD (2011b) Single- and cross-commodity discounting among cocaine addicts: the commodity and its temporal location determine discounting rate. Psychopharmacology 217(2):177–187
Bickel WK, Yi R, Landes RD, Hill PF, Baxter C (2011c) Remember the future: working memory training decreases delay discounting among stimulant addicts. Biol Psychiatry 69(3):260–265
Bickel WK, Johnson MW, Koffarnus MN, MacKillop J, Murphy JG (2014) The behavioral economics of substance use disorders: reinforcement pathologies and their repair. Annu Rev Clin Psychol 10:641–677
Bickel WK, Mellis AM, Snider SE, Moody L, Stein JS, Quisenberry AJ (2016a) Novel therapeutics for addiction: behavioral economic and neuroeconomic approaches. Curr Treat Options Psychiatry 3:277–292. https://doi.org/10.1007/s40501-016-0088-3
Bickel WK, Snider SE, Quisenberry AJ, Stein JS, Hanlon CA (2016b) Competing neurobehavioral decision systems theory of cocaine addiction: from mechanisms to therapeutic opportunities. Prog Brain Res 223:269–293
Bickel WK, Wilson AG, Chen C, Koffarnus MN, Franck CT (2016c) Stuck in time: negative income shock constricts the temporal window of valuation spanning the future and the past. PLoS One 11(9):e0163051

Bickel WK, Stein JS, Moody LN, Snider SE, Mellis AM, Quisenberry AJ (2017) Toward narrative theory: interventions for reinforcer pathology in health behavior. In: Nebraska symposium on motivation, pp 227–267

Brevet-Aeby C, Brunelin J, Iceta S, Padovan C, Poulet E (2016) Prefrontal cortex and impulsivity: interest of noninvasive brain stimulation. Neurosci Biobehav Rev 71:112–134

Brooks SJ, Wiemerslage L, Burch KH, Maiorana SA, Cocolas E, Schiöth HB et al (2017) The impact of cognitive training in substance use disorder: the effect of working memory training on impulse control in methamphetamine users. Psychopharmacology 234(12):1911–1921

Brunoni AR, Sampaio-Junior B, Moffa AH, Aparício LV, Gordon P, Klein I et al (2019) Noninvasive brain stimulation in psychiatric disorders: a primer. Braz J Psychiatry 41(1):70–81

Bulley A, Gullo MJ (2017) The influence of episodic foresight on delay discounting and demand for alcohol. Addict Behav 66:1–6

Chiou W-B, Wu W-H (2017) Episodic future thinking involving the nonsmoking self can induce lower discounting and cigarette consumption. J Stud Alcohol Drugs 78(1):106–112

Cho SS, Koshimori Y, Aminian K, Obeso I, Rusjan P, Lang AE et al (2015) Investing in the future: stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. Neuropsychopharmacology 40(3):546–553

Clewett D, Luo S, Hsu E, Ainslie G, Mather M, Monterosso J (2014) Increased functional coupling between the left fronto-parietal network and anterior insula predicts steeper delay discounting in smokers. Hum Brain Mapp 35:3774–3787. https://doi.org/10.1002/hbm.22436

Contreras-Rodríguez O, Albein-Urios N, Perales JC, Martínez-Gonzalez JM, Vilar-López R, Fernández-Serrano MJ et al (2015) Cocaine-specific neuroplasticity in the ventral striatum network is linked to delay discounting and drug relapse. Addiction 110:1953–1962. https://doi.org/10.1111/add.13076

Daniel TO, Stanton CM, Epstein LH (2013a) The future is now: comparing the effect of episodic future thinking on impulsivity in lean and obese individuals. Appetite 71:120–125

Daniel TO, Stanton CM, Epstein LH (2013b) The future is now: reducing impulsivity and energy intake using episodic future thinking. Psychol Sci 24(11):2339–2342

Daniel TO, Said M, Stanton CM, Epstein LH (2015) Episodic future thinking reduces delay discounting and energy intake in children. Eat Behav 18:20–24

DeHart WB, Odum AL (2015) The effects of the framing of time on delay discounting. J Exp Anal Behav 103(1):10–21

DeHart WB, Friedel JE, Lown JM, Odum AL (2016) The effects of financial education on impulsive decision making. PLoS One 11(7):e0159561

Deshpande HU, Mellis AM, Lisinski JM, Stein JS, Koffarnus MN, Paluch R et al (2019) Reinforcer pathology: common neural substrates for delay discounting and snack purchasing in prediabetics. Brain Cogn 132:80–88

Domínguez-Salas S, Díaz-Batanero C, Lozano-Rojas OM, Verdejo-García A (2016) Impact of general cognition and executive function deficits on addiction treatment outcomes: systematic review and discussion of neurocognitive pathways. Neurosci Biobehav Rev 71:772–801

Dshemuchadse M, Scherbaum S, Goschke T (2013) How decisions emerge: action dynamics in intertemporal decision making. J Exp Psychol Gen 142:93–100. https://doi.org/10.1037/a0028499

Elton A, Smith CT, Parrish MH, Boettiger CA (2017) Neural systems underlying individual differences in intertemporal decision-making. J Cogn Neurosci 29(3):467–479

Felton JW, Collado A, Ingram KM, Doran K, Yi R (2019) Improvement of working memory is a mechanism for reductions in delay discounting among mid-age individuals in an urban medically underserved area. Ann Behav Med 53(11):988–998. https://doi.org/10.1093/abm/kaz010

Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, Fehr E, Weber EU (2010) Lateral prefrontal cortex and self-control in intertemporal choice. Nat Neurosci 13(5):538–539

Finn PR (2002) Motivation, working memory, and decision making: a cognitive-motivational theory of personality vulnerability to alcoholism. Behav Cogn Neurosci Rev 1(3):183–205

Foxcroft DR, Coombes L, Wood S, Allen D, Almeida Santimano NML, Moreira MT (2016) Motivational interviewing for the prevention of alcohol misuse in young adults. Cochrane Database Syst Rev 7:CD007025

Friedel JE, DeHart WB, Madden GJ, Odum AL (2014) Impulsivity and cigarette smoking: discounting of monetary and consumable outcomes in current and non-smokers. Psychopharmacology 231(23):4517–4526

Gentile ND, Librizzi EH, Martinetti MP (2012) Academic constraints on alcohol consumption in college students: a behavioral economic analysis. Exp Clin Psychopharmacol 20(5):390–399

Gilbert LJ, Murphy JG, Dennhardt AA (2014) A behavioral economic analysis of the effect of next-day responsibilities on drinking. Psychol Addict Behav 28(4):1253–1258

Gould TJ (2010) Addiction and cognition. Addict Sci Clin Pract 5(2):4–14

Gregg GS (1991) Self-representation: life narrative studies in identity and ideology. Praeger, New York

Griffiths A, Hill R, Morgan C, Rendell PG, Karimi K, Wanagaratne S, Curran HV (2012) Prospective memory and future event simulation in individuals with alcohol dependence. Addiction 107(10):1809–1816

Haushofer J, Schunk D, Fehr E (2013) Negative income shocks increase discount rates. Retrieved from Working Paper website: http://www.princeton.edu/joha/publications/Haushofer_et_al_Negative_Income_Shocks_2013.pdf

Heffernan TM (2008) The impact of excessive alcohol use on prospective memory: a brief review. Curr Drug Abuse Rev 1(1):36–41

Hermans HJM (1993) The dialogical self: meaning as movement. Academic Press, San Diego

Huth AG, de Heer WA, Griffiths TL, Theunissen FE, Gallant JL (2016) Natural speech reveals the semantic maps that tile human cerebral cortex. Nature 532(7600):453–458

Insel TR (2014) The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. Am J Psychiatry 171(4):395–397

Jimura K, Myerson J, Hilgard J, Keighley J, Braver TS, Green L (2011) Domain independence and stability in young and older adults' discounting of delayed rewards. Behav Process 87 (3):253–259

Kaplan BA, Reed DD, Jarmolowicz DP (2016) Effects of episodic future thinking on discounting: personalized age-progressed pictures improve risky long-term health decisions. J Appl Behav Anal 49(1):148–169

Kaplan BA, Foster RNS, Reed DD, Amlung M, Murphy JG, MacKillop J (2018) Understanding alcohol motivation using the alcohol purchase task: a methodological systematic review. Drug Alcohol Depend 191:117–140

Kirby KN (2009) One-year temporal stability of delay-discount rates. Psychon Bull Rev 16 (3):457–462

Kirby KN, Petry NM, Bickel WK (1999) Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. J Exp Psychol Gen 128(1):78–87

Klapproth F (2012) The date-delay framing effect in temporal discounting depends on substance abuse. Behav Process 90(3):420–423

Klimas J, Field C-A, Cullen W, O'Gorman CSM, Glynn LG, Keenan E et al (2012) Psychosocial interventions to reduce alcohol consumption in concurrent problem alcohol and illicit drug users. Cochrane Database Syst Rev 11:CD009269

Koffarnus MN, Bickel WK (2014) A 5-trial adjusting delay discounting task: accurate discount rates in less than one minute. Exp Clin Psychopharmacol 22(3):222–228

Koffarnus MN, Jarmolowicz DP, Mueller ET, Bickel WK (2013) Changing delay discounting in the light of the competing neurobehavioral decision systems theory: a review. J Exp Anal Behav 99 (1):32–57

Krippner S, Bova M, Gray L (2007) Healing stories: the use of narrative in counseling and psychotherapy. Puente Publication, Charlottesville

Kurczek J, Wechsler E, Ahuja S, Jensen U, Cohen NJ, Tranel D, Duff M (2015) Differential contributions of hippocampus and medial prefrontal cortex to self-projection and self-referential processing. Neuropsychologia 73:116–126
Lahav E, Rosenboim M, Shavit T (2015) Financial literacy's effect on elicited subjective discount rate. Econ Bull 35(2):1360–1368
Lawyer SR, Schoepflin FJ (2013) Predicting domain-specific outcomes using delay and probability discounting for sexual versus monetary outcomes. Behav Process 96:71–78
Leboeuf RA (2006) Discount rates for time versus dates: the sensitivity of discounting to time-interval description. J Mark Res 43(1):59–72
Lemley SM, Kaplan BA, Reed DD, Darden AC, Jarmolowicz DP (2016) Reinforcer pathologies: predicting alcohol related problems in college drinking men and women. Drug Alcohol Depend 167:57–66
Lempert KM, Speer ME, Delgado MR, Phelps EA (2017) Positive autobiographical memory retrieval reduces temporal discounting. Soc Cogn Affect Neurosci 12(10):1584–1593
Lin H, Epstein LH (2014) Living in the moment: effects of time perspective and emotional valence of episodic thinking on delay discounting. Behav Neurosci 128(1):12–19
MacKillop J (2016) The behavioral economics and neuroeconomics of alcohol use disorders. Alcohol Clin Exp Res 40(4):672–685
MacKillop J, Miranda R Jr, Monti PM, Ray LA, Murphy JG, Rohsenow DJ et al (2010a) Alcohol demand, delayed reward discounting, and craving in relation to drinking and alcohol use disorders. J Abnorm Psychol 119(1):106–114
MacKillop J, O'Hagen S, Lisman SA, Murphy JG, Ray LA, Tidey JW et al (2010b) Behavioral economic analysis of cue-elicited craving for alcohol. Addiction 105(9):1599–1607
MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, Munafò MR (2011) Delayed reward discounting and addictive behavior: a meta-analysis. Psychopharmacology 216(3):305–321
MacKillop J, Brown CL, Stojek MK, Murphy CM, Sweet L, Niaura RS (2012) Behavioral economic analysis of withdrawal- and cue-elicited craving for tobacco: an initial investigation. Nicotine Tob Res 14(12):1426–1434
Magen E, Dweck CS, Gross JJ (2008) The hidden-zero effect: representing a single choice as an extended sequence reduces impulsive choice. Psychol Sci 19(7):648–649
McAdams DP (1988) Power, intimacy, and the life story: personological inquiries into identity. Guilford Press, New York
McAdams DP, Josselson R, Lieblich A (2006) Identity and story: creating self in narrative. American Psychological Association, Washington, DC
McClure SM, Laibson DI, Loewenstein G, Cohen JD (2004) Separate neural systems value immediate and delayed monetary rewards. Science 306(5695):503–507
McClure SM, Ericson KM, Laibson DI, Loewenstein G, Cohen JD (2007) Time discounting for primary rewards. J Neurosci 27(21):5796–5804
McLeod J (1997) Narrative and psychotherapy. Sage, London
Meier ST (2012) Language and narratives in counseling and psychotherapy. Springer, New York
Mellis AM, Athamneh LN, Stein JS, Sze YY, Epstein LH, Bickel WK (2018) Less is more: negative income shock increases immediate preference in cross commodity discounting and food demand. Appetite 129:155–161
Metrik J, Aston ER, Kahler CW, Rohsenow DJ, McGeary JE, Knopik VS, MacKillop J (2016) Cue-elicited increases in incentive salience for marijuana: craving, demand, and attentional bias. Drug Alcohol Depend 167:82–88
Naudé GP, Kaplan BA, Reed DD, Henley AJ, DiGennaro Reed FD (2018) Temporal framing and the hidden-zero effect: rate-dependent outcomes on delay discounting. J Exp Anal Behav 109 (3):506–519
NIDA (2005) Drug abuse and addiction: one of America's most challenging public health problems. https://archives.drugabuse.gov/publications/drug-abuse-addiction-one-americas-most-challenging-public-health-problems. Accessed 12 Sept 2019

Nielsen L, Riddle M, King JW, Aklin WM, Chen W, NIH Science of Behavior Change Implementation Team et al (2018) The NIH Science of Behavior Change Program: transforming the science through a focus on mechanisms of change. Behav Res Ther 101:3–11

Nummenmaa L, Saarimäki H, Glerean E, Gotsopoulos A, Jääskeläinen IP, Hari R, Sams M (2014) Emotional speech synchronizes brains across listeners and engages large-scale dynamic brain networks. NeuroImage 102(Pt 2):498–509

Nutt DJ, Robbins TW, Stimson GV, Ince M, Jackson A (2006) Drugs and the future: brain science, addiction and society. Elsevier, Oxford

O'Neill J, Daniel TO, Epstein LH (2016) Episodic future thinking reduces eating in a food court. Eat Behav 20:9–13

Owens MM, Gray JC, Amlung MT, Oshri A, Sweet LH, MacKillop J (2017) Neuroanatomical foundations of delayed reward discounting decision making. NeuroImage 161:261–270

Perkins KA (2009) Does smoking cue-induced craving tell us anything important about nicotine dependence? Addiction 104(10):1610–1616

Peters J, Büchel C (2010) Episodic future thinking reduces reward delay discounting through an enhancement of prefrontal-mediotemporal interactions. Neuron 66(1):138–148

Petry NM (2001) Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. Psychopharmacology 154(3):243–250

Radu PT, Yi R, Bickel WK, Gross JJ, McClure SM (2011) A mechanism for reducing delay discounting by altering temporal attention. J Exp Anal Behav 96(3):363–385

Rando K, Hong K-I, Bhagwagar Z, Li C-SR, Bergquist K, Guarnaccia J, Sinha R (2011) Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: a prospective study. Am J Psychiatr 168:183–192. https://doi.org/10.1176/appi.ajp.2010.10020233

Rass O, Schacht RL, Buckheit K, Johnson MW, Strain EC, Mintzer MZ (2015) A randomized controlled trial of the effects of working memory training in methadone maintenance patients. Drug Alcohol Depend 156:38–46

Read D, Frederick S, Orsel B, Rahman J (2005) Four score and seven years from now: the date/delay effect in temporal discounting. Manag Sci 51(9):1326–1335

Roma PG, Hursh SR, Hudja S (2016) Hypothetical purchase task questionnaires for behavioral economic assessments of value and motivation. Manag Decis Econ 37(4–5):306–323

Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M (2010) Acamprosate for alcohol dependence. Cochrane Database Syst Rev 9:CD004332

Rung JM, Madden GJ (2018) Experimental reductions of delay discounting and impulsive choice: a systematic review and meta-analysis. J Exp Psychol Gen 147(9):1349–1381

Sayette MA, Shiffman S, Tiffany ST, Niaura RS, Martin CS, Shadel WG (2000) The measurement of drug craving. Addiction 95(Suppl 2):S189–S210

Schmaal L, Goudriaan AE, Joos L, Dom G, Pattij T, van den Brink W, Veltman DJ (2014) Neural substrates of impulsive decision making modulated by modafinil in alcohol-dependent patients. Psychol Med 44(13):2787–2798

Seligman MEP, Railton P, Baumeister RF, Sripada C (2013) Navigating into the future or driven by the past. Perspect Psychol Sci 8(2):119–141

Shah AK, Mullainathan S, Shafir E (2012) Some consequences of having too little. Science 338 (6107):682–685

Sheffer CE, Mennemeier M, Landes RD, Bickel WK, Brackman S, Dornhoffer J et al (2013) Neuromodulation of delay discounting, the reflection effect, and cigarette consumption. J Subst Abus Treat 45(2):206–214

Sheffer CE, Bickel WK, Brandon TH, Franck CT, Deen D, Panissidi L et al (2018) Preventing relapse to smoking with transcranial magnetic stimulation: feasibility and potential efficacy. Drug Alcohol Depend 182:8–18

Skidmore JR, Murphy JG (2011) The effect of drink price and next-day responsibilities on college student drinking: a behavioral economic analysis. Psychol Addict Behav 25(1):57–68

Skidmore JR, Murphy JG, Martens MP (2014) Behavioral economic measures of alcohol reward value as problem severity indicators in college students. Exp Clin Psychopharmacol 22 (3):198–210

Snider SE, LaConte SM, Bickel WK (2016) Episodic future thinking: expansion of the temporal window in individuals with alcohol dependence. Alcohol Clin Exp Res 40(7):1558–1566
Snider SE, DeHart WB, Epstein LH, Bickel WK (2018a) Does delay discounting predict maladaptive health and financial behaviors in smokers? Health Psychol 38(1):21
Snider SE, Deshpande HU, Lisinski JM, Koffarnus MN, LaConte SM, Bickel WK (2018b) Working memory training improves alcohol users' episodic future thinking: a rate-dependent analysis. Biol Psychiatry Cogn Neurosci Neuroimaging 3(2):160–167
Snider SE, Mellis AM, Poe LM, Kocher MA, Turner JK, Bickel WK (2019) Reinforcer pathology: narrative of hurricane-associated loss increases delay discounting, demand, and consumption of highly palatable snacks in the obese. Psychol Addict Behav 34(1):136–146. https://doi.org/10.1037/adb0000498
Speedy J (2008) Narrative inquiry and psychotherapy. Palgrave, Hound-mills
Stein JS, Wilson AG, Koffarnus MN, Daniel TO, Epstein LH, Bickel WK (2016) Unstuck in time: episodic future thinking reduces delay discounting and cigarette smoking. Psychopharmacology 233(21–22):3771–3778
Stein JS, Tegge AN, Turner JK, Bickel WK (2018) Episodic future thinking reduces delay discounting and cigarette demand: an investigation of the good-subject effect. J Behav Med 41(2):269–276
Stewart JL, Connolly CG, May AC, Tapert SF, Wittmann M, Paulus MP (2014) Striatum and insula dysfunction during reinforcement learning differentiates abstinent and relapsed methamphetamine-dependent individuals. Addiction 109(3):460–471
Suckling J, Nestor LJ (2017) The neurobiology of addiction: the perspective from magnetic resonance imaging present and future. Addiction 112(2):360–369
Sze YY, Stein JS, Bickel WK, Paluch RA, Epstein LH (2017) Bleak present, bright future: online episodic future thinking, scarcity, delay discounting, and food demand. Clin Psychol Sci 5(4):683–697
Teeters JB, Murphy JG (2015) The behavioral economics of driving after drinking among college drinkers. Alcohol Clin Exp Res 39(5):896–904
Tiffany ST, Conklin CA (2000) A cognitive processing model of alcohol craving and compulsive alcohol use. Addiction 95(8 Suppl 2):145–153
Tschernegg M, Pletzer B, Schwartenbeck P, Ludersdorfer P, Hoffmann U, Kronbichler M (2015) Impulsivity relates to striatal gray matter volumes in humans: evidence from a delay discounting paradigm. Front Hum Neurosci 9:384
U.S. Department of Health and Human Services (HHS) (2016) Facing addiction in america: the surgeon general's report on alcohol, drugs, and health. HHS, Washington, DC
Volkow ND (2011) Principles of drug addiction treatment: a research-based guide. DIANE Publishing, Darby
Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M et al (2001) Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J Neurosci 21(23):9414–9418
Wanmaker S, Leijdesdorff SMJ, Geraerts E, van de Wetering BJM, Renkema PJ, Franken IHA (2018) The efficacy of a working memory training in substance use patients: a randomized double-blind placebo-controlled clinical trial. J Clin Exp Neuropsychol 40(5):473–486
Wesley MJ, Bickel WK (2014) Remember the future II: meta-analyses and functional overlap of working memory and delay discounting. Biol Psychiatry 75(6):435–448
White M, Epston D (1990) Narrative means to therapeutic ends. W. W. Norton & Company, New York
Wu C-Y, He G-B (2012) The effects of time perspective and salience of possible monetary losses on intertemporal choice. Soc Behav Pers 40(10):1645–1653
Yu R (2012) Regional white matter volumes correlate with delay discounting. PLoS One 7(2):e32595

Part III
Clinical Implications

Developmental Considerations for Assessment and Treatment of Impulsivity in Older Adults

Melissa Liu, Eva Argyriou, and Melissa A. Cyders

Contents

Abstract Impulsivity is an important factor in many clinical disorders, especially alcohol and substance use disorders. Most of the research on impulsivity in this domain has focused on adolescence and young adulthood, as this developmental period is characterized by onset of and escalation in alcohol and substance use, likely driven in part by brain development patterns. Although many individuals eventually "mature out" of these behaviors in middle adulthood, a critical subset of people do not. The role of impulsivity in middle-to-older adulthood, when certain individuals transition from normative to disordered substance use, has not been carefully examined. The goal of this paper is to review the literature on measuring and modifying impulsivity from adolescence through older adulthood, with a special focus on middle-to-older adulthood. We propose that impulsivity research should include data on middle-to-older adulthood as an important time of transition to disordered use. We consider how impulsivity might have unique meaning at different stages of the adult lifespan and suggest modifications for assessing and treating impulsivity in older adults.

Keywords Adulthood · Age · Alcohol use · Impulsivity · Substance use

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There is a vast literature linking impulsivity to a wide range of clinical problems (see Um et al. 2018), especially alcohol and substance use disorders (e.g., Coskunpinar et al. 2013; Dick et al. 2010; Gerard Moeller and Dougherty 2002; Verdejo-García et al. 2008). Most of this research has focused on adolescence and young adulthood, when impulsive and risky behaviors, such as alcohol and substance use (e.g., Young et al. 2002) are common. This period also corresponds with brain maturation that is thought to contribute to these behaviors (Blakemore and Robbins 2012; Casey et al. 2008; Crone and Dahl 2012). Although many individuals eventually "mature out" of these behaviors after the early 20s (Littlefield and Sher 2015; Littlefield et al. 2009), a subset of individuals do not and instead transition to problem use during middle adulthood (Heyman 2013). This later period is clinically important but has received little attention. For reasons that are not fully understood, alcohol and substance use appear to be increasing in middle-to-older adults (Breslow et al. 2017). The goal of this paper is to review the literature on measuring and modifying impulsivity from adolescence through older adulthood, with a special focus on middle-to-older adulthood. We consider how impulsivity might have different meanings at different stages of the adult lifespan and suggest specific modifications for assessing and treating impulsivity in older adults.

1 Measurement of Impulsivity

When researchers discuss and measure impulsivity, they are usually referring to one of two different levels of measurement or analysis, which, by and large, do not highly correspond (see Cyders and Coskunpinar 2011). The first is at the level of personality trait, i.e., the stable underlying construct of impulsivity, which commonly utilizes self-report questionnaires to assess a wide range of different traits, such as acting without thinking or seeking out exciting experiences (see Evenden 1999 for a full review on this topic). Because of the varied definitions across studies, Whiteside and Lynam (2001) conducted a factor analysis of existing personality-based impulsivity scales to identify the common traits assessed across these measures. The result of this analysis was the UPPS-P Impulsive Behavior Scale (Lynam et al. 2006; Whiteside and Lynam 2001). Three main domains are included in this scale: *deficits in conscientiousness*, which comprises not thinking before acting and not following tasks to completion; *sensation seeking*, which is seeking out new and exciting experiences and sensations; and *emotion-based rash action*, which comprises acting rashly in response to negative ("negative urgency") and positive ("positive urgency") emotions (see Cyders and Smith 2007; Cyders et al. 2007; Lynam et al. 2006; Whiteside and Lynam 2001).

The second level of measurement is the behavioral manifestation of the trait, i.e., assessing impulsive behavior, usually via an objective behavioral task. Behavioral measures of impulsivity seek to assess behavioral responding in the moment and thus are more "state-like" than "trait-like" (Cyders and Coskunpinar 2011; Sharma et al. 2014). Over the years, many behavioral lab tasks have been developed,

assessing different aspects of impulsivity. This field also sought to compile and group these measures into representative task domains of impulsivity. Dick et al. (2010) categorized these assessments into five domains: prepotent response inhibition (suppressing dominant or automatic responses), resistance to distractor interference (avoiding distraction in goal-directed behavior), resistance to proactive interference (avoiding memory intrusions in goal-directed behavior), delay response (choosing a larger delayed reward over an immediate reward), and distortions in elapsed time (judging passing time accurately). Others have categorized these tendencies differently (Aragues et al. 2011; Fineberg et al. 2014; Sharma et al. 2014).

Overall, objective behavioral measures of impulsivity correlate poorly with self-report measures, likely because trait-like and state-like impulsivity are different things (e.g., Cyders and Coskunpinar 2011). Importantly though, even the separate constructs *within* each measurement type are quite independent and predict differential aspects of alcohol and substance use behaviors. For example, the three UPPS-P domains only have small to moderate intercorrelations correlate with each other (Cyders and Smith 2007), suggesting they are separate, though somewhat related, tendencies toward impulsive action. Other work has supported these lower correlations among different constructs within personality-based and objective behavioral measurements of impulsivity, showing that disparate constructs differentially relate to substance use outcomes (e.g., Coskunpinar et al. 2013; Dick et al. 2010; Smith et al. 2007). Measuring impulsivity constructs at the sub-facet level leads to more precise measurement and more accurate prediction of substance use outcomes (see Smith et al. 2003, 2007).

A construct that has been formulated as distinct from impulsivity is compulsivity. Compulsivity refers to behaviors that are outside of one's control, difficult to stop, and that have become insensitive to environmental consequences of the behaviors (see Koob and Le Moal 2008). George Koob (2004) has proposed that whereas alcohol and substance addiction is driven by impulsivity at the early stages of substance use, it is controlled by compulsivity at the later stages. In this model, one moves from positive reinforcement reasons for substance use (e.g., to feel the high) to negative reinforcement motivations (e.g., to avoid withdrawal symptoms) (Koob 2004). Thus, this suggests that impulsivity is important for initiation of substance and alcohol use, but that compulsivity comes into play in the transition to a substance use disorder. This has been supported by some research where impulsivity is an important factor in substance use in adolescence and young adulthood (see reviews by Stautz and Cooper 2013; VanderVeen et al. 2016), whereas compulsivity is more important in middle-to-older adulthood as people transition to disorder-level use (e.g., Koob and Le Moal 2008). Yet, these conclusions raise questions about the operational definition of compulsivity and whether the claim that compulsivity plays a greater role later in the drug use trajectory could be confounded by the samples typically studied in impulsivity research (see a review by Argyriou et al. 2018). If the participants of studies investigating impulsivity are mainly adolescents or young adults, this may give the impression that impulsive

behaviors are more important in these younger groups, eventually biasing impulsivity-based theory. The distinction and relative importance of impulsivity vs. compulsivity in the development and maintenance of substance use disorders has recently been questioned. Zorrilla and Koob (2019) proposed that a specific impulsivity trait, namely, negative urgency, is the bridge that facilitates the transition from social or normative substance use to addiction. Indeed, meta-analytic findings indicate that negative urgency is the personality-based impulsivity trait that has the highest associations with alcohol dependence (Coskunpinar et al. 2013). Additionally, certain brain mechanisms appear to underlie both negative urgency and addiction (Um et al. 2019), further strengthening the link between this trait and addiction. Thus, focusing primarily on adolescents and young adults in studying how impulsivity underlies alcohol and substance use disorder risk may have led to a misunderstanding as to which traits underlie how addiction develops and is maintained. It has been proposed that whereas sensation seeking is important for the onset of substance use, negative urgency is more important for the transition to problematic use (Smith et al. 2007).

2 Developmental Changes in Impulsivity Across the Lifespan

Impulsivity changes across the lifespan, corresponding with maturational changes in the brain. In general, personality-based impulsivity traits increase with the onset of puberty through the early 20s and then level off in the transition into middle adulthood (Littlefield et al. 2016; Romer and Hennessy 2007; Steinberg et al. 2008), although this pattern is not as robust for sensation seeking (Collado et al. 2014; Harden and Tucker-Drob 2011; Pedersen et al. 2012). For behavioral measures, delayed reward discounting decreases from adolescence into adulthood (Green et al. 1994; Olson et al. 2007; Prencipe et al. 2011), and response inhibition performance improves from adolescence into adulthood (Jaeger 2013; López-Caneda et al. 2013). It has been suggested that the increase in impulsivity during adolescence results from the gap between the early development in the affective processing system (including areas of the mesolimbic dopamine circuit) and later development of the cognitive control system (including the lateral prefrontal cortex and parts of the anterior cingulate cortex) (Ernst and Fudge 2009; Somerville et al. 2010; Stautz and Cooper 2013; Steinberg 2008). This gap in maturation may make it difficult for adolescents to restrain impulses toward rewarding experiences, such as substance use. Another theory highlights the heightened sensitivity of a maturing "reward system" to social and affective incentives that become more salient due to a highly flexible (as opposed to underdeveloped) cognitive control system (Crone and Dahl 2012; Galván 2010).

Starting around the age of 25, impulsive and risk-taking behaviors decline, corresponding with reductions in impulsivity traits that level off in middle adulthood – a phenomenon called "maturing out" (Littlefield and Sher 2016; Vergés et al. 2012). However, a small but clinically relevant percentage of adults increases their substance use and transitions to more severe patterns of use indicative of a substance use disorder. More research is needed to understand how impulsivity may drive this maintenance or increase in problematic substance use in middle adulthood.

Limited research examining impulsivity in middle-to-older adulthood is problematic for research and clinical application. Because impulsivity has not been considered an important determinant of substance use among middle-older adults, it is not known whether impulsivity is simply understudied in this group *or* whether it is indeed less relevant for middle-to-older adults. If impulsivity plays a lesser role in substance use for older adults, or if their substance use is driven by different forms of impulsivity, this would suggest a need for different strategies for identifying, preventing, and treating this population compared to younger individuals. Applying treatments that work for younger populations to older people may be misdirected (Argyriou et al. 2018). Next, we discuss developmental considerations for the measurement and treatment of impulsivity in older adults.

3 Developmental Considerations for the Measurement of Impulsivity in Older Adults

Comparing impulsivity and its relationship with risk-taking behaviors across developmental stages depends on valid measurement of the construct across the lifespan. Normal aging is associated with cognitive, affective, and sensorimotor changes (Samanez-Larkin and Knutson 2015; Samanez-Larkin et al. 2013) that could affect not only impulsivity in older adults but also the type of impulsivity and the validity of the assessments used to measure impulsivity (Argyriou et al. 2018). For example, many behavioral impulsivity tasks rely on speed of processing, which slows with age, thus confounding the measurement of this tendency in older adults. Additionally, some personality-based scales ask about risk-taking behaviors that require a certain amount of physical agility (e.g., skydiving, riding a motorcycle) that would be more difficult as one ages. Further complicating the matter is that most of these measures were originally developed and tested in young adult, college samples; thus, it is unclear whether they are valid and reliable in middle-to-older adults. To evaluate differences in impulsivity across the lifespan, we need self-report and behavioral task measures that can provide valid and reliable assessments of impulsivity across age groups. Only then will we be able to draw valid conclusions about group differences in impulsivity across age.

Some of this work has begun. A recent study (Argyriou et al. 2019) assessed the invariance of the UPPS-P Impulsive Behavior Scale across the adult lifespan (age range: 18–85 years old) in a community sample that closely matches the US general

population based on age, sex, race, immigrant status, language, education, and income. This measurement invariance analysis tested whether the UPPS-P scale can produce valid and reliable measurements of the impulsivity traits across age. If it does, then valid comparisons can be made across age groups; if it does not, then comparisons across the adult lifespan cannot be validly made using this scale as they can lead to results that inflate, deflate, or distort the appearance of real group differences. The findings of this study generally supported the invariance of this measure across young, middle, and older adulthood. However, three items with differential item functioning were identified that are less valid indicators for impulsivity traits in older ages (e.g., Item 51: "I would like to go scuba diving"). The authors recommended removing these items for more valid comparisons of self-reported impulsivity across age (Argyriou et al. 2019). After removing these items, the authors found a small decrease in sensation seeking with age, and there were no differences in the other traits across age. Previously reported large decreases in impulsivity with age may reflect less valid measurement of impulsivity among older adults using existing scales and measures.

Assessing the applicability of behavioral tasks across the adult lifespan is more complex than with self-report measures. Performance on a behavioral measure of impulsivity may be confounded with other processes that change with normal aging. For example, for prepotent response inhibition tasks, such as the Stop Task, slower reaction time, the most commonly used index of prepotent response inhibition, could reflect aging-related slower motoric dexterity or processing speed (Charlton et al. 2008; Sebastian et al. 2013), although the task takes into account individual differences in reaction time to some extent. Older individuals may be less familiar with computer technology (Iverson et al. 2009), which could reduce the validity of using these tasks in older age groups. Stereotype threat (i.e., the fear one may have that they may perpetuate or exemplify a negative stereotype about themselves) may further affect performance disproportionately among older adults (Mazerolle et al. 2012). Thus, task performance may be affected by other factors in addition to, or instead of, impaired ability to suppress automatic responses. In the case of delay discounting tasks, there may be age-related changes in the value of the rewards or in the perception of elapsed time of the delays. Rewards in delay discounting procedures may be real or hypothetical; cognitive control mechanisms are important for hypothetical rewards, whereas affective/motivation processes are important for real rewards. Changes in motivational goals and life experience with normal aging affect the subjective value of rewards and motivation to discount it (Samanez-Larkin et al. 2013), which may change the meaning of a reward and its discounting time frame. Any of these factors might threaten the validity of the measurement and complicate direct comparisons of performance across age (Argyriou et al. 2018). Addressing these confounds that disproportionately influence older adults will result in measures of impulsivity that are suitable for comparisons across the adult lifespan.

4 Developmental Considerations for the Treatment of Impulsivity in Older Adults

Several studies have examined the relationship between impulsivity and substance use treatment outcomes. A recent meta-analysis found that high negative urgency and lack of premeditation at intake to a substance use disorder treatment program were associated with worse treatment outcomes (Hershberger et al. 2017), supported by some work (Loree et al. 2015; Stevens et al. 2014), although not others (e.g., Tomko et al. 2016). A recent review supported this idea and furthermore recommended the development of novel treatment methods to target other facets of impulsivity (Um et al. 2018).

Overall, there are few treatments specifically targeting impulsivity and fewer that have been tested, although some have made suggestions on possible treatment approaches for these tendencies. Zapolski et al. (2010) suggested that negative urgency might be effectively modified through distress tolerance strategies or emotion regulation approaches; sensation seeking may be modified through developing a bank of safe, stimulating activities that do not involve substance use; positive urgency may be modified through the teaching of adaptive techniques for savoring success and positive mood; lack of premeditation may be modified through cognitive meditation training; and lack of perseverance may be modified through stimulant medication and the use of goal setting and planning training. Tomko et al. (2016) suggested that contingency management may be a particularly effective treatment approach for those high in impulsivity.

Some researchers have developed treatments to reduce impulsivity in adolescent and young adult populations, including some with substance use problems. These studies have targeted mainly self-report, trait measures of impulsivity, which may be difficult to change. One study in a small sample of African American female college students found that training in emotion modulation decreased negative and positive urgency and reduced risk-taking (Weiss et al. 2015). Similarly, a school-based treatment based in dialectical behavioral therapy reduced risk-taking behaviors in a small sample of high school adolescents (Zapolski and Smith 2017). Interestingly, among adolescents in a smoking cessation program combining contingency management and cognitive behavioral therapy, lower impulsivity scores at treatment onset were associated with increased likelihood of successful abstinence (Krishnan-Sarin et al. 2007).

Some approaches (e.g., distress tolerance or emotion regulation to modify negative urgency) appear to be easily generalizable to older adult populations. However, several aspects of impulsivity-targeted treatments designed for youth may not be applicable for middle-to-older adults. For example, school-based interventions (e.g., the treatment tested by Zapolski and Smith 2017) would be difficult to modify for older adults, because the content may not generalize, the time involved is large (9-week session), and the school setting may not have a comparable counterpart. Older adults might be treated in a work setting, but the viability of this option is limited by stigma, availability, and the trade-off between work time and the time

spent in group. Additionally, it would be difficult to identify adults to refer to such a treatment. In contrast to school-based interventions, the emotion modulation approach supported by Weiss et al. (2015) may be better suited to adults, as the content is delivered in an 1-hour session, which could be administered via more accessible strategies (e.g., webinar, online module, orientation meeting).

It is not clear whether reducing impulsivity would be effective in middle-to-older adults. Of note, the meta-analysis conducted by Hershberger et al. (2017) reviewed studies examining substance use disorder treatment effectiveness, not impulsivity in particular. These studies reported greater age ranges than typically included in impulsivity research, thus allowing for a better understanding of how treatment may affect and may be affected by impulsivity. Although Hershberger et al. (2017) did not examine age as a moderator of treatment effectiveness (due to the limited number of studies that met inclusion criteria), the effects reported (that negative urgency and lack of premeditation reduced treatment effectiveness) were found in treatment samples with a mean age of approximately 35 years of age (ranges from mid-20s to mid-40s), indicating that, at least, the findings suggesting the influence of impulsivity on substance use disorder treatment outcomes likely apply to young-to-middle adults. They additionally reported significant, but very small, reductions in negative urgency and sensation seeking during treatment (Hershberger et al. 2017).

5 Suggestions for Measurement and Treatment of Impulsivity in Older Adults

We thus suggest that, although promising, existing measurements of and treatments for impulsivity may need to be modified extensively to maximize their effectiveness in middle-to-older adults. Previous attempts to modify psychological treatment with older adults have been proposed (e.g., Knight et al. 2003). We use the framework provided by Evans (2007) to suggest how to modify assessment and treatment of impulsivity for older adults, including addressing cognitive changes, addressing sensory impairment, incorporating physical health limitations, utilizing flexible settings and formats, and modifying content.

Addressing Cognitive Changes Cognitive changes may confound behavioral measures of impulsivity in older adults (see review by Argyriou et al. 2018), reducing the valid measurement of these tendencies in this group. Additionally, many of the approaches suggested by Zapolski et al. (2010) utilize teaching and applying new skills (e.g., emotion regulation, distress tolerance, goal setting) through psychoeducation and practice. Impairments in memory may reduce the effectiveness of such approaches. Similar to what is suggested by Evans (2007), using memory training and aids and ensuring the presentations of information in multiple formats can help increase the application of existing treatments to older populations. For instance, assistive devices, such as written handouts and online

modules, may ease the stress of taking notes or recalling key components after intervention sessions (Foulk et al. 2014).

Addressing Sensory Impairment Visual and hearing impairment can limit the validity of any self-report or behavioral measure of impulsivity and can also limit the effectiveness of any treatment training, sometimes without awareness. Assessing for such impairment prior to assessment and treatment planning is important so that modifications can be made to address any identified impairments (e.g., larger font, more contrast between stimuli and background during behavioral tasks, audio narration, etc.).

Incorporating Physical Health Limitations Physical limitations may limit self-report and behavioral measurement of impulsivity – for example, an older person may say "no" to the item "I would enjoy water skiing" because physical limitations would make the activity unpleasant, not because they are low in sensation seeking (see Argyriou et al. 2018). Additionally, treatments that aim to develop appropriate behavioral substitutions for impulsive behaviors will be somewhat limited by the physical health of the individual – for example, relaxation techniques may be difficult in those with many physical ailments or replacement behaviors may not all be possible for the individual. Additionally, physical ailments can cause serious stress, complicating treatment because of additional symptomology, pain management, and the impact of medical treatment and medication. Thus, we suggest including a measure of physical health, discussing limitations with the client, and including feedback from the participant as to the feasibility of homework assignments.

Utilizing Flexible Settings and Format Settings and formats used for adolescent and younger adult populations often include school or university settings, increasing availability and feasibility of treatment. Middle-to-older adults likely have additional barriers with attending treatment including limited time and resources (e.g., childcare or eldercare responsibilities, long work hours, transportation limitations). Flexible settings for treatment (e.g., treatment in own home or in primary care settings, Evans (2007); online or phone interventions) and reduced time commitments will likely increase access to care for these groups. Treatment sessions can also be shortened (i.e., from 60 min to 30 min) or incorporate breaks as needed. Additionally, some data suggest that group treatments may be more effective for older adults, as it provides peer support and opportunities to try new skills (Evans 2007; Foulk et al. 2014). Using this intervention format may also lower financial barriers since it is covered by Medicare and most private insurance.

Modifying Content Some of the measurement or therapy content for impulsivity may not generalize well to older adults. For example, what impulsivity is in older adults may look quite different than in younger adults – with less reliance on traditional risk taking (e.g., sky diving, bungee jumping) and more reliance on behaviors still available to an aging population (e.g., unprotected sex, investments) – which may make traditional impulsivity measures less valid in older adults. Additionally, there is often a view that people are "too old to change," both by the

therapist and the client, that may need to be challenged early on in treatment for it to be most effective (Evans 2007). Evans (2007) also reviews other important considerations for treatment with older adults including ageist assumptions, stigma, and prejudice against younger therapists, all of which would need to be targeted in treatment.

6 Conclusions

In conclusion, extensive literature supports impulsivity as a significant risk factor in substance use. However, more needs to be done to fully extend this across the lifespan, particularly in how best to modify assessment and treatment of impulsivity in older adults. Because of the varied time course of substance use, we propose that impulsivity research should move away from a predominant focus on adolescence and young adulthood to also include data on middle-to-older adulthood as an important time of transition to disordered use. Over-reliance on adolescents and young adults has likely led to an underappreciation of the role impulsivity may play among middle-to-older adults. Additionally, although some evidence suggests that self-report impulsivity measures can validly assess impulsivity across the adult lifespan (e.g., Argyriou et al. 2019), researchers may want to rethink how we use behavioral tasks to assess impulsivity in these older groups, as performance is likely confounded with aging-related effects. Valid comparisons across the lifespan cannot be made until it is documented that the measures used to assess impulsivity produce valid and reliable data across age. Applying treatments designed to modify impulsivity to older adults requires consideration of important modifications in order to increase usefulness and effectiveness. We hope to catalyze work with impulsivity in middle-to-older adults. If impulsivity is fundamentally different in older adults or differentially impacts substance use or treatment outcomes, we require age-specific strategies for identification, prevention, and treatment to effectively reduce risks in this clinically relevant group.

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References

Aragues M, Jurado R, Quinto R, Rubio G (2011) Laboratory paradigms of impulsivity and alcohol dependence: a review. Eur Addict Res 17:64. https://doi.org/10.1159/000321345

Argyriou E, Um M, Carron C, Cyders M (2018) Age and impulsive behavior in drug addiction: a review of past research and future directions. Pharmacol Biochem Behav 164:106–117. https://doi.org/10.1016/j.pbb.2017.07.013

Argyriou E, Um M, Wu W, Cyders MA (2019) Measurement invariance of the UPPS-P impulsive behavior scale across age and sex across the adult life span. Assessment. https://doi.org/10.1177/1073191119832660

Blakemore SJ, Robbins TW (2012) Decision-making in the adolescent brain. Nat Neurosci 15:1184. https://doi.org/10.1038/nn.3177

Breslow RA, Castle I-JP, Chen CM, Graubard BI (2017) Trends in alcohol consumption among older Americans: national health interview surveys, 1997 to 2014. Alcohol Clin Exp Res 41:976–986

Casey BJ, Jones RM, Hare TA (2008) The adolescent brain. Ann N Y Acad Sci 1124:111. https://doi.org/10.1196/annals.1440.010

Charlton RA, Landau S, Schiavone F, Barrick TR, Clark CA, Markus HS, Morris RG (2008) A structural equation modeling investigation of age-related variance in executive function and DTI measured white matter damage. Neurobiol Aging 29(10):1547–1555

Collado A, Felton JW, Macpherson L, Lejuez CW (2014) Longitudinal trajectories of sensation seeking, risk taking propensity, and impulsive behavior across early to middle adolescence. Addict Behav 39:1580–1588. https://doi.org/10.1016/j.addbeh.2014.01.024

Coskunpinar A, Dir AL, Cyders MA (2013) Multidimensionality in impulsivity and alcohol use: a meta-analysis using the UPPS model of impulsivity. Alcohol Clin Exp Res 37(9):1441–1450. https://doi.org/10.1111/acer.12131

Crone EA, Dahl RE (2012) Understanding adolescence as a period of social-affective engagement and goal flexibility. Nat Rev Neurosci 13:636. https://doi.org/10.1038/nrn3313

Cyders MA, Coskunpinar A (2011) Measurement of constructs using self-report and behavioral lab tasks: is there overlap in nomothetic span and construct representation for impulsivity? Clin Psychol Rev 31(6):965–982. https://doi.org/10.1016/j.cpr.2011.06.001

Cyders MA, Smith GT (2007) Mood-based rash action and its components: positive and negative urgency. Personal Individ Differ 43:839–850

Cyders MA, Smith GT, Spillane NS, Fischer S, Annus AM, Peterson C (2007) Integration of impulsivity and positive mood to predict risky behavior: development and validation of a measure of positive urgency. Psychol Assess 19(1):107–118. https://doi.org/10.1037/1040-3590.19.1.107

Dick DM, Smith G, Olausson P, Mitchell SH, Leeman RF, O'Malley SS, Sher K (2010) Understanding the construct of impulsivity and its relationship to alcohol use disorders. Addict Biol 15:217. https://doi.org/10.1111/j.1369-1600.2009.00190.x

Ernst M, Fudge JL (2009) A developmental neurobiological model of motivated behavior: anatomy, connectivity and ontogeny of the triadic nodes. Neurosci Biobehav Rev 33(3):367–382

Evans C (2007) Cognitive–behavioural therapy with older people. Adv Psychiatr Treat 13 (2):111–118

Evenden JL (1999) Varieties of impulsivity. Psychopharmacology 146:348. https://doi.org/10.1007/PL00005481

Fineberg NA, Chamberlain SR, Goudriaan AE, Stein DJ, Vanderschuren LJMJ, Gillan CM et al (2014) New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. CNS Spectr 19:69

Foulk MA, Ingersoll-Dayton B, Kavanagh J, Robinson E, Kales HC (2014) Mindfulness-based cognitive therapy with older adults: an exploratory study. J Gerontol Soc Work 57(5):498–520

Galván A (2010) Adolescent development of the reward system. Front Hum Neurosci 4:6

Gerard Moeller F, Dougherty DM (2002) Impulsivity and substance abuse: what is the connection? Addict Disord Treat 1:3. https://doi.org/10.1097/00132576-200205000-00002

Green L, Fry AF, Myerson J (1994) Discounting of delayed rewards: a life-span comparison. Psychol Sci 5(1):33–36

Harden KP, Tucker-Drob EM (2011) Individual differences in the development of sensation seeking and impulsivity during adolescence: further evidence for a dual systems model. Dev Psychol 47(3):739

Hershberger AR, Um M, Cyders MA (2017) The relationship between the UPPS-P impulsive personality traits and substance use psychotherapy outcomes: a meta-analysis. Drug Alcohol Depend 178:408–416
Heyman GM (2013) Quitting drugs: quantitative and qualitative features. Annu Rev Clin Psychol 9:29. https://doi.org/10.1146/annurev-clinpsy-032511-143041
Iverson GL, Brooks BL, Ashton VL, Johnson LG, Gualtieri CT (2009) Does familiarity with computers affect computerized neuropsychological test performance? J Clin Exp Neuropsychol 31(5):594–604
Jaeger A (2013) Inhibitory control and the adolescent brain: a review of fMRI research. Psychol Neurosci 6(1):23–30
Knight BG, Nordhus IH, Satre DD (2003) Psychotherapy with older adults. Handbook Psychol 453–468
Koob GF (2004) Allostatic view of motivation: implications for psychopathology. Nebr Symp Motiv 50:1–18
Koob GF, Le Moal M (2008) Addiction and the brain antireward system. Annu Rev Psychol 59 (1):29–53. https://doi.org/10.1146/annurev.psych.59.103006.093548
Krishnan-Sarin S, Reynolds B, Duhig AM, Smith A, Liss T, McFetridge A et al (2007) Behavioral impulsivity predicts treatment outcome in a smoking cessation program for adolescent smokers. Drug Alcohol Depend 88(1):79–82
Littlefield AK, Sher KJ (2015) Alcohol use disorders in young adulthood. In: Young adult mental health. https://doi.org/10.1093/med:psych/9780195332711.003.0018
Littlefield AK, Sher KJ (2016) 10 personality and substance use disorders. In: The Oxford handbook of substance use and substance use disorders: two-volume set, p 351
Littlefield AK, Sher KJ, Wood PK (2009) Is "maturing out" of problematic alcohol involvement related to personality change? J Abnorm Psychol 118(2):360–374. https://doi.org/10.1037/a0015125
Littlefield AK, Stevens AK, Ellingson JM, King KM, Jackson KM (2016) Changes in negative urgency, positive urgency, and sensation seeking across adolescence. Personal Individ Differ 90:332–337
López-Caneda E, Rodríguez Holguín S, Cadaveira F, Corral M, Doallo S (2013) Impact of alcohol use on inhibitory control (and vice versa) during adolescence and young adulthood: a review. Alcohol Alcohol 49(2):173–181
Loree AM, Lundahl LH, Ledgerwood DM (2015) Impulsivity as a predictor of treatment outcome in substance use disorders: review and synthesis. Drug Alcohol Rev 34(2):119–134
Lynam DR, Smith GT, Whiteside SP, Cyders MA (2006) The UPPS-P: assessing five personality pathways to impulsive behavior. Purdue University, West Lafayette
Mazerolle M, Régner I, Morisset P, Rigalleau F, Huguet P (2012) Stereotype threat strengthens automatic recall and undermines controlled processes in older adults. Psychol Sci 23 (7):723–727
Olson EA, Hooper CJ, Collins P, Luciana M (2007) Adolescents' performance on delay and probability discounting tasks: contributions of age, intelligence, executive functioning, and self-reported externalizing behavior. Personal Individ Differ 43(7):1886–1897
Pedersen SL, Molina BS, Belendiuk KA, Donovan JE (2012) Racial differences in the development of impulsivity and sensation seeking from childhood into adolescence and their relation to alcohol use. Alcohol Clin Exp Res 36(10):1794–1802
Romer D, Hennessy M (2007) A biosocial-affect model of adolescent sensation seeking: the role of affect evaluation and peer-group influence in adolescent drug use. Prev Sci 8(2):89
Samanez-Larkin GR, Knutson B (2015) Decision making in the ageing brain: changes in affective and motivational circuits. Nat Rev Neurosci 16(5):278
Samanez-Larkin GR, Li SC, Ridderinkhof KR (2013) Complementary approaches to the study of decision making across the adult life span. Front Neurosci 7:243
Sebastian A, Baldermann C, Feige B, Katzev M, Scheller E, Hellwig B et al (2013) Differential effects of age on subcomponents of response inhibition. Neurobiol Aging 34(9):2183–2193

Sharma L, Markon KE, Clark LA (2014) Toward a theory of distinct types of "impulsive" behaviors: a meta-analysis of self-report and behavioral measures. Psychol Bull 140:374. https://doi.org/10.1037/a0034418

Smith GT, Fischer S, Fister SM (2003) Incremental validity principles in test construction. Psychol Assess 15:467. https://doi.org/10.1037/1040-3590.15.4.467

Smith GT, Fischer S, Cyders MA, Annus AM, Spillane NS, McCarthy DM (2007) On the validity and utility of discriminating among impulsivity-like traits. Assessment 14:155–170. https://doi.org/10.1111/1744-7941.12061

Somerville LH, Jones RM, Casey BJ (2010) A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. Brain Cogn 72(1):124–133

Stautz K, Cooper A (2013) Impulsivity-related personality traits and adolescent alcohol use: a meta-analytic review. Clin Psychol Rev 33(4):574–592. https://doi.org/10.1016/j.cpr.2013.03.003

Steinberg L (2008) A social neuroscience perspective on adolescent risk-taking. Dev Rev 28 (1):78–106

Steinberg L, Albert D, Cauffman E, Banich M, Graham S, Woolard J (2008) Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: evidence for a dual systems model. Dev Psychol 44(6):1764

Stevens L, Verdejo-García A, Goudriaan AE, Roeyers H, Dom G, Vanderplasschen W (2014) Impulsivity as a vulnerability factor for poor addiction treatment outcomes: a review of neurocognitive findings among individuals with substance use disorders. J Subst Abus Treat 47(1):58–72

Tomko RL, Bountress KE, Gray KM (2016) Personalizing substance use treatment based on pre-treatment impulsivity and sensation seeking: a review. Drug Alcohol Depend 167:1–7

Um M, Whitt ZT, Revilla R, Hunton T, Cyders MA (2019) Shared neural correlates underlying addictive disorders and negative urgency. Brain Sci 9(2):36

Um M, Hershberger AR, Whitt ZT, Cyders MA (2018) Recommendations for applying a multi-dimensional model of impulsive personality to diagnosis and treatment. Borderline Personal Disord Emot Dysregul 5:6. https://doi.org/10.1186/s40479-018-0084-x

VanderVeen JD, Hershberger AR, Cyders MA (2016) UPPS-P model impulsivity and marijuana use behaviors in adolescents: a meta-analysis. Drug Alcohol Depend 168:181. https://doi.org/10.1016/j.drugalcdep.2016.09.016

Verdejo-García A, Lawrence AJ, Clark L (2008) Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. Neurosci Biobehav Rev 32:777. https://doi.org/10.1016/j.neubiorev.2007.11.003

Vergés A, Jackson KM, Bucholz KK, Grant JD, Trull TJ, Wood PK, Sher KJ (2012) Deconstructing the age-prevalence curve of alcohol dependence: why "maturing out" is only a small piece of the puzzle. J Abnorm Psychol 121(2):511

Weiss NH, Tull MT, Davis LT, Searcy J, Williams I, Gratz KL (2015) A preliminary experimental investigation of emotion dysregulation and impulsivity in risky behaviours. Behav Chang 32 (2):127–142

Whiteside SP, Lynam DR (2001) The five factor model and impulsivity: using a structural model of personality to understand impulsivity. Personal Individ Differ 30(4):669–689. https://doi.org/10.1016/S0191-8869(00)00064-7

Young SE, Corley RP, Stallings MC, Rhee SH, Crowley TJ, Hewitt JK (2002) Substance use, abuse and dependence in adolescence: prevalence, symptom profiles and correlates. Drug Alcohol Depend 68:309. https://doi.org/10.1016/S0376-8716(02)00225-9

Zapolski TC, Smith GT (2017) Pilot study: implementing a brief DBT skills program in schools to reduce health risk behaviors among early adolescents. J Sch Nurs 33(3):198–204

Zapolski TC, Settles RE, Cyders MA, Smith GT (2010) Borderline personality disorder, bulimia nervosa, antisocial personality disorder, ADHD, substance use: common threads, common treatment needs, and the nature of impulsivity. Indep Pract 30(1):20

Zorrilla EP, Koob GF (2019) Impulsivity derived from the dark side: neurocircuits that contribute to negative urgency. Front Behav Neurosci 13. https://doi.org/10.3389/fnbeh.2019.00136

Impulsivity and Suicidal Behavior

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Abstract Suicide is the leading cause of injury mortality in the United States and the second-leading cause of death in people aged 10–34 years. While many long-term risk factors are known, the short-term prediction of suicidal behavior remains elusive. Many characteristics of suicidal behavior cut across diagnoses, but suicide is increased in recurrent psychiatric disorders, addictive disorders, and trauma-related disorders. Suicide results from the interaction of short-term and long-term behavioral regulation. The shorter the time-course of the mechanism, the closer it is to actual suicidal behavior, and the harder it is to prevent. We will discuss the manner in which impulsivity, a major determinant of short-term suicide risk, interacts with longer-term risk factors, especially sensitization to addictive or traumatic stimuli. Impulsivity predisposes to sensitization; in turn, impulsivity is a prominent component of sensitized behavior. Impulsivity can be described as a general pattern of behavior ("trait" impulsivity), as responses that are not conformed to their context (action-impulsivity), or as inability to delay reward or to take future consequences into account (choice-impulsivity). Each of these contributes to suicidal behavior. The neural mechanisms of impulsivity and sensitization are analogous, and sensitization can produce rapidly fluctuating patterns of impulsive behavior, arousal, and anhedonia. In order to recognize and prevent suicidal behavior, it is necessary to identify factors associated with susceptibility to bouts of impulsive behavior in people at elevated long-term risk.

Keywords Arousal · Behavioral sensitization · Impulsive behavior · Suicide

"The man who, in a fit of melancholy, kills himself today, would have wished to live had he waited a week" Voltaire, "Cato," Philosophical Dictionary 1764)

1 Introduction

Impulsivity has been defined as a pattern of action occurring without ability to adapt it to its context or consequences (Moeller et al. 2001). Suicide would appear to a definitive impulsive act, but, in general, suicide attempts have planned and non-planned components. For example, jumping from the Golden Gate Bridge is a highly lethal form of suicide attempt with roughly 1760 attempts and 40 survivals (Suicides at the Golden Gate Bridge 1999). Interviews of attempters who survived, and evidence from those who did not, reveal an admixture of impulsivity and planning. We will discuss the manner in which mechanisms of immediate behavioral control, underlying impulsivity, interact with earlier events and longer-term behavioral mechanisms in suicidal behavior. Rather than a dichotomy of impulsive and non-impulsive suicide attempts, impulsivity is generally a component of suicidal behavior, even when there is a plan. Mechanisms of impulsive behavior itself, and of

regulating the susceptibility to impulsivity, are basic to suicidal behavior and its prevention.

Suicide is the leading cause of injury mortality in the United States and is increasing, while other injury mortality is not (Heron 2019). Death by suicide exceeds motor vehicle accidents or homicides (Heron 2019). Suicide is the cause of death in about 10% of individuals with affective disorders, post-traumatic stress disorder (PTSD), substance and alcohol use disorders (SUD), or schizophrenia (Chesney et al. 2014; Oquendo and Baca-Garcia 2014; Obegi 2019; Beghi et al. 2013; Fenton 2000; Bronisch and Wittchen 1994) and is the second-leading cause of death in people between 10 and 34 years of age in the United States (Heron 2019).

This paper will focus on relationships between suicidal behavior and the regulation of action. Underlying principles are that (1) suicidal behavior represents interaction of long-term and immediate behavior regulation, culminating in fluctuating increases in impulsivity (Lijffijt et al. 2018); (2) these risks and mechanisms for suicide, including aggression, impulsivity, and susceptibility to hopelessness, may define a suicide-susceptible group across diagnoses, providing trans-diagnostic measures of lifetime risk for potentially lethal suicide attempts and targets for prevention (Chesney et al. 2014; Oquendo and Baca-Garcia 2014; Obegi 2019; Beghi et al. 2013; Fenton 2000); and (3) identifying members of this high-risk group can underlie effective long-term, preventive strategies for suicide.

Properties of suicidal behaviors include (1) suicide is a common cause of death in relevant populations but is a relatively rare event over limited populations and durations, making potential treatments difficult to evaluate; (2) there are indicators of lifetime and long-term risk of suicide, but prediction of short-term risk is far more difficult; and (3) indicators of risk most widely used as "proxies" for suicide are usually related to suicide attempts, but almost 60% of suicides are first attempts (Bostwick et al. 2016). Impulsive behavior may appear hard to predict, but it may be even more challenging to predict varying susceptibility to impulsive behavior.

2 Time Structure of Suicidal Behavior: "A Fit of Melancholy"

Even in individuals with high long-term risk, suicidal behavior, strongly related to "fits of melancholy (Voltaire, "Cato," Philosophical Dictionary 1764)," is difficult to predict. Further, this only describes half the challenge. The other half is the fact that, after surviving or avoiding an attempt, the same person remains at risk for future "fits of melancholy" (Chesney et al. 2014). We will discuss interactions between long- and short-term behavior regulation that may predispose to this risk and strategies to address the challenges that result. The first of these is to identify individuals at risk for a "fit of melancholy," which requires understanding of potential mechanisms.

2.1 Suicide Risk Characteristics

Medically severe suicide attempts (*MSSA* (Potter et al. 1998) generally defined as injury requiring hospital treatment) *indicate high risk for suicide and other premature mortality and may identify a population with generally high risk for bouts of severely impulsive behavior*. In medically severe attempters followed for 5 years, all-cause mortality was increased 15-fold in men and ninefold in women, including increased mortality from homicide and accidents; risk of suicide mortality was over 1,400-fold higher than that for the general population (Ostamo and Lonnqvist 2001). Risk was highest during the first year (Ostamo and Lonnqvist 2001; Nordstrom et al. 1995) and persisted for over 10 years (Nordstrom et al. 1995; Suokas et al. 2001). Posthospital survival time correlated negatively with trait impulsivity (Nordstrom et al. 1996). Since 60% of premature mortality was not suicide (Potter et al. 1998), medically severe attempters appear to have high general post-attempt mortality risk consistent with susceptibility to impulsive behavior (Suokas et al. 2001).

2.2 High-Risk Behavior Combines Activation and Depression Across Diagnoses

Combined depressive and manic symptoms were associated with impulsivity, hopelessness, hostility, and suicidal behavior more than either alone (Swann et al. 2009a). Impulsivity (both questionnaire- and laboratory-measured) and suicidality correlated with mania scores in depressed patients (Swann et al. 2007). Impulsivity predisposes to hopelessness (Swann et al. 2008) and can dissociate hopelessness from depressed mood (Simon et al. 2001). Impulsivity (Corruble et al. 1999) or severe anxiety (Korn et al. 1997) predicted suicide risk in depression, reflecting the association between impulsivity and activation or hyperarousal (Barratt and Patton 1983). The relationship between impulsivity and arousal regulation is nonlinear, leading to variations in behavior control that are difficult to predict (Zhang et al. 2015). Across diagnoses, activated depression, combining impulsivity and hopelessness, increases risk of suicide (Lijffijt et al. 2018; Simon et al. 2001; Swann et al. 2009b). This is related to the behavioral construct of negative urgency, the predisposition to impulsive behavior during negative affective states (Cyders and Smith 2008). The interaction of negative affect, loss of impulse control, and hyperarousal is central to suicidal behavior regardless of diagnosis (Lijffijt et al. 2018; Korn et al. 1997; Barratt and Patton 1983; Zhang et al. 2015; Swann et al. 2009b; Doihara et al. 2012).

Suicidal behavior occurs across diagnoses (Chesney et al. 2014; Oquendo and Baca-Garcia 2014; Obegi 2019; Beghi et al. 2013) and can occur in individuals without a conventionally defined major psychiatric disorder (Chesney et al. 2014; Oquendo and Baca-Garcia 2014). This has led to the proposal that suicide or severe suicidal behavior is a specific illness that can, but need not, be combined with conventionally defined psychiatric disorders and the designation of suicidal behavior

disorder as a potential entity for further study in DSM5 (Oquendo and Baca-Garcia 2014; Obegi 2019). As noted above, most excess mortality after MSSA appears related to action control but is not suicide, and individuals with recent MSSA have increased general mortality and functional impairment (Suokas et al. 2001). It is, therefore, likely that the putative illness contributing to suicidal behavior has severe consequences related to impaired regulation of behavior in general, extending beyond suicide.

Impulsivity and Suicidal Behavior Suicides are categorized as impulsive or non-impulsive, but this can be a false dichotomy: trait impulsivity was higher in individuals with both a plan and an attempt than with either an attempt or plan alone (Ribeiro et al. 2015); "impulsive" individuals are more likely to act on a "planned" attempt, and state-dependent impulsivity during depressive episodes increases suicide risk (Swann et al. 2007; Witte et al. 2008). Depression/hopelessness and activation/impulsivity interact in risk: the more severe one is, the less severity is required in the other. Activation can arise quickly and sporadically during ongoing depression; similarly, dysphoria, hopelessness, or anhedonia can arise during manic states (Voltaire, "Cato," Philosophical Dictionary 1764), with hyperarousal as a central component (Lijffijt et al. 2018; Doihara et al. 2012). Carefully made plans can lie dormant until circumstances elicit impairment of behavioral control (Doihara et al. 2012; Witte et al. 2008).

3 Short-Term Indices of Behavioral and Affective Regulation: Endogenous or Exogenous Stressors Increase Risk for Activation and Suicidal Behavior

3.1 Impulsivity Encompasses Distinct Behavioral Models and Adaptations

Impulsivity is an imbalance between initiation and inhibition of action (Barratt and Patton 1983; Swann et al. 2005a). It can be measured as:

1. *A "trait," or relatively stable personality and attitude characteristic*, generally used questionnaires such as the Barratt Impulsiveness Scale (Barratt and Patton 1983), or the Urgency, (Lack of) Premeditation, (Lack of) Perseverance, Sensation seeking, and Positive urgency (UPPS-P) Scale (Cyders and Smith 2008). While these questionnaire measures are often regarded as traits, they can change over time (Corruble et al. 1999), with a prominent nonlinear relationship to changes in arousal (Zhang et al. 2015). Negative urgency, or impulsivity combined with depressive affect, may be especially germane to stress sensitization and suicidal behavior (Swann et al. 2009b). Therefore, elevated BIS-11 scores or UPPS negative urgency scores raise the potential for arousal-related and time-

limited emergence of "state-dependent" impulsivity and may be increased in suicide attempters across diagnosis (Doihara et al. 2012).

2. *Quantitative behavioral laboratory measures of inability to regulate activation or inhibition of behavior:*

   - Reduced ability to adequately appraise stimuli or their context before responding (action- or rapid-response impulsivity (Swann et al. 2009b; Dougherty et al. 2003a; Swann et al. 2002; Hamilton et al. 2015a; Swick et al. 2012; Bjork et al. 2004)). Action-impulsivity can be measured as commission errors on continuous performance tests that control for attention (Dougherty et al. 2003a; Swann et al. 2002; Hamilton et al. 2015a). Commission (impulsive) errors and accelerated reaction times are associated with impulsive and risky behavior, increased in PTSD (Swick et al. 2012), SUD (Bjork et al. 2004), schizophrenia (Enticott et al. 2008), patients with complicated bipolar disorder (Swann et al. 2009b) and their siblings (Doyle et al. 2009), and combined disorders (Swann et al. 2004; Dougherty et al. 2004). Action-impulsivity is increased with history of severe suicidal behavior, with (Swann et al. 2005a) or without (Dougherty et al. 2004) bipolar disorder. Action-impulsivity is familial (Dougherty et al. 2003b), stress-related (Schepis et al. 2011), increased by NE (Swann et al. 2013a), and related to impaired neurophysiological responses preceding conscious awareness (Lijffijt et al. 2009; Swann et al. 2013b).
   - Reduced ability to withhold response for a delayed larger reward over an immediate smaller one (choice- or reward-delay impulsivity; or delay-discounting) (Swann et al. 2002; Hamilton et al. 2015b; Hyten et al. 1994; Ho et al. 1999). Choice-impulsivity reflects inability to incorporate the future into decisions, predisposing toward suicidal behavior during short-term adversity (Hamilton et al. 2015b).

These aspects of impulsive behavior are increased in bipolar disorder (Swann et al. 2009b, 2013b), schizophrenia (Enticott et al. 2008; Lee et al. 2013), depressive disorders (Takahashi et al. 2008; Henna et al. 2013), addictive disorders (Moeller et al. 2002), trauma-related disorders (Swick et al. 2012), and people at high familial risk (Sanches et al. 2014). Advantages of laboratory measures or impulsivity include behavioral specificity, lack of recall bias, and animal analogues for translational studies. They measure evoked impulsive responding in a person who may appear stable, so they represent the potential for impulsive behavior in response to an acute stimulus.

Table 1 shows measures of risk for impulsive behavior and examples of circumstances that may elicit impulsivity and arousal in susceptible individuals. Emergence of any of the factors in the right column can increase suicide risk, especially when combined with depressed affect.

Impulsivity and Suicide We studied impulsivity, alcohol use, and clinical characteristics in self-inflicted gunshot wounds with helicopter rescue (Peterson et al. 1985), and a CDC/NIAAA-funded case-control study of MSSA at Level I trauma

Table 1 Characteristics of risk for emergence of impulsivity

Quantitative measures of risk (Dougherty et al. 2003a; Swann et al. 2002; Hamilton et al. 2015a, 2015b; Hyten et al. 1994; Ho et al. 1999)	Examples of risk factors for emergence of impulsive action
– Immediate memory task commission errors and reaction times – Stop-signal or analogous behavior inhibition tasks: increased stop-signal reaction time; commission errors	– Hyperarousal, sleep disruption, stressors, overstimulation – Pharmacological agents (prescribed or not) that produce behavioral disinhibition or facilitate overstimulation

centers (Potter et al. 1998). Nearly lethal attempts, even if planned, were associated with increased action-impulsivity; impulsivity may increase the likelihood of carrying out a "planned" attempt (Simon et al. 2001; Swann et al. 2005a). Predominately impulsive attempters had relatively low expectation to die but more violent methods; elevated hopelessness similar to predominately premeditated attempters, but normal depression scores similar to community controls (Simon et al. 2001). Impulsivity, with low perseverance, resilience, and future sense (Barratt and Patton 1983), can be, operationally, hopelessness without depressed mood. Impulsivity increases activation and hopelessness, doubling its impact on suicidality.

3.2 Endogenous or Exogenous Stressors Can Increase NE and Risk for Activation and Suicidality

Prefrontal cortex function requires balance between alpha-1 and alpha-2 NE receptor effects (Arnsten et al. 1999; Berridge and Waterhouse 2003). Stressful or addictive stimuli, partially via α1-NE receptors, impair inhibitory prefrontal cortex (PFC) function, resulting in associated with impulsivity and activation (Arnsten 1997). NE reuptake blockade increases synaptic NE, but firing rate and NE release are reduced via alpha-2-mediated feedback inhibition (Aghajanian 1978), stabilizing NE. NE release elicited by stress or by blockade of alpha-2 NE receptors impairs prefrontal cortex inhibitory functions (Arnsten and Li 2005; Fitzgerald 2011). NE increases action-impulsivity in animals (Sun et al. 2010) and humans (Swann et al. 2005b, 2013a). Behavioral effects can include anxiety and panic (Gurguis and Uhde 1990), manic symptoms (Price et al. 1984; Swann et al. 1987), and post-traumatic intrusive or hyperarousal-related phenomena (Southwick et al. 1993; Pardon et al. 2002).

Action-impulsivity in controls given the alpha-2 antagonist yohimbine (increased impulsive response errors, accelerated reaction time, impulsive response bias (Swann et al. 2013a; Swann et al. 2005b)) resembles that in subjects with bipolar disorder and MSSA (Swann et al. 2005a) and correlates with increased NE metabolite levels (Swann et al. 2013a). Increased activation and PFC inhibition by NE may disrupt the activation-inhibition balance that can protect against suicide.

Action-impulsivity correlates with impaired sensory gating (Lijffijt et al. 2009), a neurophysiological measure of pre-attentive behavioral inhibition, bypassing conscious behavioral control. Action-impulsivity can be measured by EEG as disinhibited early responses to stimuli (Lijffijt et al. 2009; Swann et al. 2013b) and impaired error correction and monitoring (Ruchsow et al. 2005) and by computer tests measuring response inhibition (Dougherty et al. 2003a; Swann et al. 2002; Hamilton et al. 2015a). Choice-impulsivity, which is increased in bipolar disorder combined with antisocial personality disorder (Swann et al. (2011), can be measured by computer tests of ability to delay reward (Hamilton et al. 2015b; Hyten et al. 1994; Ho et al. 1999).

4 In Susceptible Individuals, Stressful or Rewarding Stimuli Produce Sensitization with Increased Susceptibility to Unstable, Impulsive Behavior and Negative Urgency

Repeated stimulants (Robinson and Becker 1986; Predy and Kokkindis 1984) or stressors (Haile et al. 2001) produce behavioral sensitization and cross-sensitization (Bonate et al. 1997; Yang et al. 2003; Miczek et al. 1999). This requires dopaminergic D2 (Kuczenski and Segal 2001), alpha-1 noradrenergic (Drouin et al. 2002), nicotinic (DiFranza and Wellman 2007; Schoffelmeer et al. 2002), and glutamate (Wolfe 1998) receptor stimulation, results in NE-5HT uncoupling (Salomon et al. 2006) and reduced serotonin in anterior cingulate cortex (ACC) (Heidbreder et al. 1999). Once established, sensitization can generalize across stimulus classes. Cross-sensitization between stressors and stimulant administration has been demonstrated in humans (Booij et al. 2016).

Rats (Alttoa et al. 2007) or humans (Boileau et al. 2006) with high impulsivity are more readily sensitized. Sensitization, in turn, increases impulsivity (Swann et al. 2009b; Paine et al. 2003) and stress-induced anhedonia (Rygula et al. 2005). A parallel relationship may exist with arousal; high arousal associated with the sensitizing stimulus (perhaps related to salience) may facilitate susceptibility to sensitization (Lijffijt et al. 2018). Sensitized behavior is associated with rapidly fluctuating arousal and disinhibition (Jones et al. 2013; Anderson and Revelle 1994). Susceptibility to sensitization is ongoing. Cumulative adversity, a measure of allostatic load, increases alcohol drinking, mediated by trait impulsivity (Hamilton et al. 2013), and sensitizes neural responses to acute stressors (Seo et al. 2014). Behavioral sensitization, from early trauma, substance use, or illness episodes, predisposes to stress-induced arousal, impulsivity, and anhedonia (Paine et al. 2003; Rygula et al. 2005), potentially increasing suicide risk.

4.1 *Action-Impulsivity as a Latent Trait Predisposing to Suicidality*

Individuals with uncomplicated bipolar disorder have elevated action-impulsivity during mania (Swann et al. 2003), especially if combined with depression, but not otherwise (Swann et al. 2007, 2009a, 2009b). Action-impulsivity is elevated, however, in euthymic subjects with bipolar disorder and SUD history (Dougherty et al. 2004). Further, action-impulsivity is elevated (increased commission errors and accelerated reaction time) in euthymic subjects with many episodes of illness, independent of SUD history (F (Voltaire, "Cato," Philosophical Dictionary 1764; DiFranza and Wellman 2007)=11.1, $p = 0.001$), suggesting that sensitizing factors like severe recurrence or SUD convert potential action-impulsivity from state-dependent to trait-like (Swann et al. 2009b). Figure 1 shows the manner in which sensitization to stressors, addictive stimuli, or episodes creates the potential for sensitized behavior. This behavior can lie dormant until stress-related hyperarousal, either associated with re-stimulus (with the initial stimulus-type or via cross-sensitization) or some other source of salient hyperarousal occurs. This can lead to active expression of the latent trait. In bipolar disorder, a condition associated with varying susceptibility to sensitization, action-impulsivity was increased with MSSA history (but not with less severe suicide attempts), even after correction for SUD, in

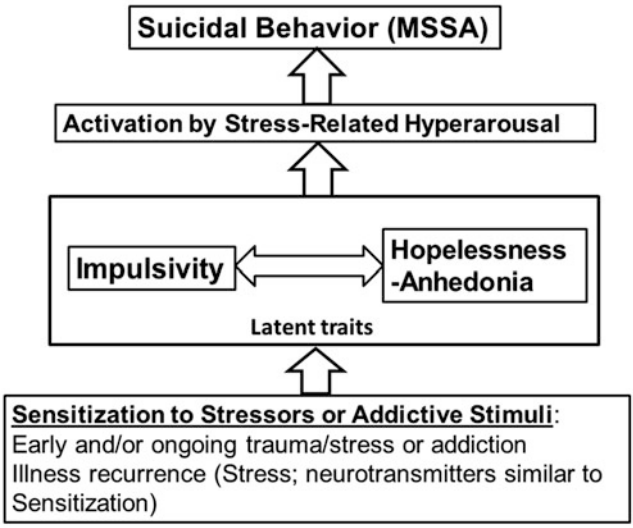

Fig. 1 Interaction of sensitization, arousal, and impulsivity. Sensitization to stressors, addictive stimuli, or other factors, such as illness episodes, which appear to have similar neurochemical effects, appears to elicit potentially exaggerated responses to sensitizing stimuli or to stress-related arousal. This includes prominent impulsivity, often accompanied by anhedonia, with potential for suicidal behavior. However, this potential behavioral response may lie dormant for an unpredictable period before a suitable stimulus elicits the latent behavior

stable subjects with bipolar disorder evaluated over a year after the index suicide attempt (Swann et al. 2005a). In a stepwise logistic regression model of behavioral and clinical characteristics and MSSA, action-impulsivity predicted 86.8% of cases (Swann et al. 2005a). Results were similar across diagnoses (Dougherty et al. 2004). Activated depression was related to action-impulsivity and suicide attempt history (Swann et al. 2007, 2009a). Action-impulsivity, or a related characteristic, appears to be potentially activated in susceptible individuals who have been exposed to a behaviorally sensitizing stimulus. This sensitization-related impulsivity is related in a complex manner to arousal, resulting in fluctuations in behavior that can be difficult to predict (Zhang et al. 2015; Jones et al. 2013; Anderson and Revelle 1994).

4.2 Suicide and Near-Instantaneous Behavior Regulation

Acute suicidal behavior is hard to predict (Voltaire, "Cato," Philosophical Dictionary 1764; Fartacek et al. 2016; Scocco et al. n.d.; Deisenhammer et al. 2009; Depp et al. 2016; Kleiman et al. 2017), arising rapidly and often dissipating rapidly, if transiently, with interventions (such as emergency room or hospital admissions). Risk for suicide, across diagnoses, is increased with addiction (Powell et al. 2001) or trauma (Guina et al. 2017), impulsivity (Nordstrom et al. 1996; Swann et al. 2005a, 2007, 2009a, 2009b; Ribeiro et al. 2015), impulsive aggression (Coryell et al. 2018), affective instability (Zhang et al. 2015; Swann et al. 2009b), and psychosocial instability, stressors, or isolation (Suokas et al. 2001; Ribeiro et al. 2015). Risk for suicidal behavior is associated with conditions with long- and short-term instability. Evidence from prospective and retrospective studies has shown that the prediction of immediate suicide risk is difficult even in those at high risk:

1. Medical records showed that 72% of suicide attempts were “unpreventable” based on (a) clinical observations by patients’ clinicians shortly before the behavior and (b) blinded record review (Scocco et al. n.d.).
2. Studies of specific events found that the time elapsed between the first consideration of a specific suicidal act and the overt suicidal behavior averaged about 10 min (Deisenhammer et al. 2009) regardless of how much time had elapsed since the underlying suicidal plan and creating challenges for interventions.
3. Consistent with the relationship between negative affect and impulsivity (negative urgency) in suicidal behavior, ecological momentary assessment in suicidal individuals showed a pattern where increased negative affect led to increased impulsivity (Depp et al. 2016).
4. Ecological momentary assessment studies have shown that suicidal ideation/intent varies rapidly and unpredictably. Baseline suicidal ideation correlated with related constructs such as hopelessness, but rapid changes in suicidal ideation did not correlate with changes in the other behavioral constructs (Kleiman et al. 2017).

5. Suicidal ideation results from interactions across short- and long-term processes, resulting in the essentially chaotic course demonstrated by ecological momentary assessment (Fartacek et al. 2016).

5 Summary: Determinants of Impulsivity Expression and Targets for Treatment

Relationships between suicidal behavior and impulsivity develop over time in a complex manner. A central characteristic is the emergence of susceptibility to arousal- or stress-based impulsivity. As the time courses of mechanisms become shorter, acute risk for suicidal behavior increases, and predictability of behavior decreases:

1. Lifetime: genetic susceptibility to characteristics associated with behavior and affective dyscontrol including affective, psychotic, stress/trauma-related, addictive, and "personality" disorders (Chesney et al. 2014).
2. Long-term and potentially lifetime: prenatal or early exposure to sensitizing addictive or traumatic symptoms (Henry et al. 1995). Early exposure exaggerates effects of later repeated or chronic exposure (Seo et al. 2014).
3. Prodrome of a disorder listed in (1), when increased trait-impulsivity is already likely although diagnostic features are not yet present (Doyle et al. 2009; Sanches et al. 2014).
4. Action- and choice-impulsivity, increased, as dormant traits, by exposure to sensitizing stimuli, including stressors, addictive stimuli, or other situations (such as psychiatric illness episodes (Swann et al. 2009b)) with increased stimulation of noradrenergic, dopaminergic, and/or glutamatergic receptors in someone who was previously sensitized. The dormant trait is potentially expressed with re-exposure to analogues of sensitizing stimuli, or recurrence of episodes.
5. Impulsive behavior triggered by interaction between latent action-impulsivity and negative arousal or stress. This behavior is difficult to predict and can fluctuate markedly during periods of risk (Jones et al. 2013).

6 Conclusions

Susceptibility to suicidal behavior involves an interaction between characteristics regulating rapid responses to stimuli, which take place over long periods, and the responses themselves, which can occur almost instantaneously. The neural circuitry involved in rapid responses (impulsivity) is similar to that of a more persistent response, behavioral sensitization. Clinical data shows that sensitization produces measurable changes in evoked impulsivity before spontaneously impulsive behavior occurs (Swann et al. 2005a, 2009b). The interaction of multiple processes with

different time courses results in a potential propensity for “fits of melancholy” (Voltaire, "Cato," Philosophical Dictionary 1764), in which negative arousal can emerge quickly and unpredictably in an individual who has been sensitized to stressors, addictive stimuli, and/or illness episodes. Elegant methods, such as ecological momentary assessment, are potential measures of these rapid responses (Fartacek et al. 2016; Kleiman et al. 2017). However, detecting and treating these ephemeral but dangerous states may not be a practical primary strategy (Deisenhammer et al. 2009). It may be more practical to detect the susceptibility to these states and treat them preventively. An integrated strategy could involve (1) detecting susceptibility to action dysregulation using behavioral and neurophysiological measures described above and documenting response to challenge with an agent, such as lithium, that could improve immediate action control on a long-term basis; and (2) combining lithium-like long-term preventive treatment with ketamine-like short-term rescue treatment. This would address the manner in which impulsivity is governed, in an ongoing manner, by remote and instantaneous stimuli.

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References

Aghajanian GK (1978) Feedback regulation of central monoaminergic neurons: evidence from single cell recording studies. Essays Neurochem Neuropharmacol 3:1–32

Alttoa A, Eller M, Herm L, Rinken A, Harro J (2007). Amphetamine-induced locomotion, behavioral sensitization to amphetamine, and striatal D2 receptor function in rats with high or low spontaneous exploratory activity: differences in the role of locus coeruleus. Brain Res 1131 [1]:138–148.

Anderson KJ, Revelle W (1994) Impulsivity and time of day: is rate of change in arousal a function of impulsivity? J Pers Soc Psychol 67(2):334–344

Arnsten AFT (1997) Catecholaminergic regulation of the prefrontal cortex. J Psychopharmacol 11:151–162

Arnsten AF, Li BM (2005) Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 57(11):1377–1384

Arnsten AF, Mathew R, Ubriani R, Taylor JR, Li BM (1999) Alpha-1 noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. Biol Psychiatry 45(1):26–31

Barratt ES, Patton JH (1983) Impulsivity: cognitive, behavioral, and psychophysiological correlates. In: Zuckerman M (ed) Biological basis of sensation-seeking, impulsivity, and anxiety. Lawrence Erlbaum Associates, Hillsdale, pp 77–116

Beghi M, Rosenbaum JF, Cerri C, Cornaggia CM (2013) Risk factors for fatal and nonfatal repetition of suicide attempts: a literature review. Neuropsychiatr Dis Treat 9:1725–1736

Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev 42(1):33–84

Bjork JM, Hommer DW, Grant SJ, Danube C (2004) Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1-/type 2-like traits. Alcohol 34(2–3):133–150

Boileau I, Dagher A, Leyton M, Gunn RN, Baker GB, Diksic M, Benkelfat C (2006) Modeling sensitization to stimulants in humans: an [11C]raclopride/positron emission tomography study in healthy men. Arch Gen Psychiatry 63(12):1386–1395

Bonate PL, Swann A, Silverman PB (1997) Context-dependent cross-sensitization between cocaine and amphetamine. Life Sci 60:PL1–PL7

Booij L, Welfeld K, Leyton M, Dagher A, Boileau I, Sibon I, Baker GB, Diksic M, Soucy J-P, Pruessner JC, Cawley-Fiset E, Casey KF, Benkelfat C (2016) Dopamine cross-sensitization between psychostimulant drugs and stress in healthy male volunteers. Trans Psychiatry 6:740

Bostwick JM, Pabbati C, Geske JR, McKean AJ (2016) Suicide attempt as a risk factor for completed suicide: even more lethal than we knew. Am J Psychiatr 173(11):1094–1100

Bronisch T, Wittchen HU (1994) Suicidal ideation and suicide attempts: comorbidity with depression, anxiety disorders, and substance abuse disorder. Eur Arch Psychiatry Clin Neurosci 244:93–98

Chesney E, Goodwin GG, Fazel S (2014) Risk of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 13:153–160

Corruble E, Damy C, Guelfi JD (1999) Impulsivity: a relevant dimension in depression regarding suicide attempts? J Affect Disord 53(3):211–215

Coryell W, Evans SJ, Pandey GN, Jones-Brando L, Dickerson F, Yolken R (2018) Aggression, impulsivity and inflammatory markers as risk factors for suicidal behavior. J Psychiatry Res 106:38–42

Cyders MA, Smith GT (2008) Emotion-based dispositions to rash action: positive and negative urgency. Psychol Bull 134:801–808

Deisenhammer EA, Ing CM, Strauss R, Kemmler G, Hinterhuber H, Weiss EM (2009) The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? J Clin Psychiatry 70:19–24

Depp CA, Moore RC, Dev SI, Mausbach BT, Eyler LT, Granholm EL (2016) The temporal course and clinical correlates of subjective impulsivity in bipolar disorder as revealed through ecological momentary assessment. J Affect Disord 193:145–150

DiFranza JR, Wellman RJ (2007) Sensitization to nicotine: how the animal literature might inform future human research. Nicotine Tob Res 9:9–20

Doihara C, Kawanishi C, Ohyama N, Yamada T, Nakagawa M, Iwamoto Y, Odawara T, Hirayasu Y (2012) Trait impulsivity in suicide attempters: preliminary study. Psychiatry Clin Neurosci 66 (6):529–532

Dougherty DM, Bjork JM, Harper RA, Marsh DM, Moeller FG, Mathias CW, Swann AC (2003a) Behavioral impulsivity paradigms: a comparison in hospitalized adolescents with disruptive behavior disorders. J Child Psychol Psychiatry 44:1145–1157

Dougherty DM, Bjork JM, Moeller FG, Harper RA, Marsh DM, Mathias CW, Swann AC (2003b) Familial transmission of Continuous Performance test behavior: attentional and impulsive response characteristics. J Gen Psychol 130(1):5–21

Dougherty DM, Mathias CW, Marsh DM, Papageorgiou TD, Swann AC, Moeller FG (2004) Laboratory-measured behavioral impulsivity relates to suicide attempt history. Suicide Life Threat Behav 34:374–385

Doyle AE, Wozniak J, Wilens TE, Henin A, Seidman LJ, Petty C, Fried R, Gross LM, Faraone SV, Biederman J (2009) Neurocognitive impairment in unaffected siblings of youth with bipolar disorder. Psychol Med 39(8):1253–1263

Drouin C, Darracq L, Trovero F, Blanc G, Glowinski J, Cotecchia S, Tassin JP (2002) Alpha1b-adrenergic receptors control locomotor and rewarding effects of psychostimulants and opiates. J Neurosci 22(7):2873–2884

Enticott PG, Ogloff JR, Bradshaw JL (2008) Response inhibition and impulsivity in schizophrenia. Psychiatry Res 157(1-3):251–439

Fartacek C, Schiepek G, Kunroth S, Fartacek R, Ploder M (2016) Real-time monitoring of nonlinear suicidal dynamics: methodology and a demonstrative case report. Front Psych 7:1–14

Fenton WS (2000) Depression, suicide, and suicide prevention in schizophrenia. Suicide Life Threat Behav 30(1):34–49

Fitzgerald PJ (2011) A neurochemical yin and yang: does serotonin activate and norepinephrine deactivate the prefrontal cortex? Psychopharmacology 213(2–3):171–182

Guina J, Nahhas RW, Mata N, Farnsworth S (2017) Which post-traumatic stress disorder symptoms, trauma types, and substances correlate with suicide attempts in trauma survivors? Prim Care Companion CNS Disord 95(5). https://doi.org/10.4088/PCC.17m02177

Gurguis GN, Uhde TW (1990) Plasma 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) and growth hormone responses to yohimbine in panic disorder patients and normal controls. Psychoneuroendocrinology 15(3):217–224

Haile CN, GrandPre T, Kosten TA (2001) Chronic unpredictable stress, but not chronic predictable stress, enhances the sensitivity to the behavioral effects of cocaine in rats. Psychopharmacology 154(2):213–220

Hamilton KR, Ansell EB, Reynolds B, Potenza MN, Sinha R (2013) Self-reported impulsivity, but not behavioral choice or response impulsivity, partially mediates the effect of stress on drinking behavior. Stress 16(1):3–15

Hamilton KR, Littlefield AK, Anastasio NC, Cunningham KA, Fink LH, Wing VC, Mathias CW, Lane SD, Schutz C, Swann AC, Lejuez CW, Clark L, Moeller FG, Potenza MN (2015a) Rapid-response impulsivity: definitions, measurement issues, and clinical implications. Personal Disord Theory Res Treat 6:169–181

Hamilton KR, Mitchell MR, Wing VC, Balodis IM, Bickel W, Fillmore M, Lane SD, Lejuez CW, Littlefield AK, Luijten M, Mathias CW, Mitchell SH, Napier TC, Reynolds B, Schütz CG, Setlow B, Sher KJ, Swann AC, Tedford SE, White MJ, Winstanley C, Yi R, Potenza MN, Moeller FG (2015b) Choice impulsivity: definitions, measurement issues, and clinical implications. Personal Disord Theory Res Treat 6:182–198

Heidbreder CA, Oertle T, Feldon J (1999) Dopamine and serotonin imbalances in the left anterior cingulate and pyriform cortices following the repeated intermittent administration of cocaine. Neuroscience 89(3):701–715

Henna E, Hatch JP, Nicoletti M, Swann AC, Zunta-Soares G, Soares JC (2013) Is impulsivity a common trait in bipolar and unipolar disorders? Bipolar Disord 15:223–227

Henry C, Guegant G, Cador M, Arnauld E, Arsaut J, Le Moal M, Demotes-Mainard J (1995) Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbens. Brain Res 685(1–2):179–186

Heron MP (2019) Deaths: leading causes for 2017. Natl Vital Stat Rep 68(6):1–77

Ho MY, Mobini S, Chiang T-J, Bradshaw CM, Szabadi E (1999) Theory and method in the quantitative analysis of "impulsive choice" behaviour: implications for psychopharmacology. Psychopharmacology 146:362–372

Hyten C, Madden GJ, Field DP (1994) Exchange delays and impulsive choice in humans. J Exp Anal Behav 62:225–233

Jones A, Christiansen P, Nederkoorn C, Houben K, Field M (2013) Fluctuating disinhibition: implications for the understanding and treatment of alcohol and other substance use disorders. Front Psychiatry 4:140

Kleiman EM, Turner BJ, Fedor S, Beale EE, Huffman JC, Nock MK (2017) Examination of real-time fluctuations in suicidal ideation and its risk factors: results from two ecological momentary assessment studies. J Abnorm Psychol 126:726–738

Korn ML, Plutchik R, van Praag HM (1997) Panic-associated suicidal and aggressive ideation and behavior. J Psychiatr Res 31(4):481–487

Kuczenski R, Segal DS (2001) Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine. J Pharmacol Exp Ther 296(3):876–883

Lee TY, Kim SN, Jang JH, Shim G, Jung WH, Shin NY et al (2013) Neural correlate of impulsivity in subjects at ultra- high risk for psychosis. Prog Neuro-Psychopharmacol Biol Psychiatry 45:165–169

Lijffijt M, Lane SD, Meier SL, Boutros NN, Burroughs S, Steinberg JL, Moeller FG, Swann AC (2009) P50, N100, and P200 sensory gating: relationships with behavioral inhibition, attention, and working memory. Psychophysiology 46(5):1059–1068

Lijffijt M, O'Brien B, Salas R, Mathew SJ, Swann AC (2018) Interactions of immediate and long-term action regulation in the course and complications of bipolar disorder. Philos Trans R Soc Part B. https://doi.org/10.1098/RSTB.2018.0132
Miczek KA, Nikulina E, Kream RM, Carter G, Espejo EF (1999) Behavioral sensitization to cocaine after a brief social defeat stress: c-fos expression in the PAG. Psychopharmacology 141(3):225–234
Moeller FG, Barratt ES, Dougherty DM, Schmitz J, Swann AC (2001) Psychiatric aspects of impulsivity. Am J Psychiatr 158:1783–1793
Moeller FG, Dougherty DM, Barratt ES, Oderinde V, Mathias CW, Harper RA, Swann AC (2002) Increased impulsivity in cocaine dependent subjects independent of antisocial personality disorder and aggression. Drug Alcohol Depend 68(1):105–111
Nordstrom P, Samuelsson M, Asberg M (1995) Survival analysis of suicide risk after attempted suicide. Acta Psychiatr Scand 91(5):336–409
Nordstrom P, Gustavsson P, Edman G, Asberg M (1996) Temperamental vulnerability and suicide risk after attempted suicide. Suicide Life Threat Behav 26(4):380–394
Obegi JH (2019) Rethinking suicidal behavior disorder. Crisis 40:209–219
Oquendo MA, Baca-Garcia E (2014) Suicidal behavior disorder as a diagnostic entity in the DSM5 classification system: advantages outweigh limitations. World Psychiatry 3:1–6
Ostamo A, Lonnqvist J (2001) Excess mortality of suicide attempters. Soc Psychiatry Psychiatr Epidemiol 36(1):29–35
Paine TA, Dringenberg HC, Olmstead MC (2003) Effects of chronic cocaine on impulsivity: relation to cortical serotonin mechanisms. Behav Brain Res 147(1–2):135–147
Pardon MC, Gould GG, Garcia A, Phillips L, Cook MC, Miller SA, Mason PA, Morilak DA (2002) Stress reactivity of the brain noradrenergic system in three rat strains differing in their neuroendocrine and behavioral responses to stress: implications for susceptibility to stress-related neuropsychiatric disorders. Neuroscience 115(1):229–242
Peterson LG, Peterson M, O'Shanick G, Swann AC (1985) Violent suicide attempts: lethality of method vs. intent. Am J Psychiatry 142:228–230
Potter LB, Kresnow M, Powell KE, O'Carroll PW, Lee RK, Frankowski RF, Swann AC, Bayer TL, Bautista MH, Briscoe MG (1998) Identification of nearly fatal suicide attempts: self-inflicted injury severity form. Suicide Life Threat Behav 28(2):174–186
Powell KE, Kresnow M-J, Mercy JA, Potter LB, Swann AC, Frankowski RF, Lee RK, Bayer TL (2001) Alcohol consumption and nearly lethal suicide attempts. Suicide Life Threat Behav 32 (suppl):30–41
Predy PA, Kokkindis L (1984) Sensitization to the effects of repeated amphetamine administration on intracranial self-stimulation: evidence for changes in reward processes. Behav Brain Res 13 (3):251–259
Price LH, Charney DS, Heninger GR (1984) Three cases of manic symptoms following yohimbine administration. Am J Psychiatry 141:1267–1268
Ribeiro JD, Yen S, Joiner T, Siegler IC (2015) Capability for suicide interacts with states of heightened arousal to predict death by suicide beyond the effects of depression and hopelessness. J Affect Disord 188:53–59
Robinson TE, Becker JB (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res 396(2):157–198
Ruchsow M, Spitzer M, Gron G, Grothe J, Kiefer M (2005) Error processing and impulsiveness in normals: evidence from event-related potentials. Brain Res Cogn Brain Res 24(2):317–325
Rygula R, Abumaria N, Flugge G, Fuchs E, Ruther E, Havemann-Reinecke U (2005) Anhedonia and motivational deficits in rats: impact of chronic social stress. Behav Brain Res 162 (1):127–134
Salomon L, Lanteri C, Glowinski J, Tassin JP (2006) Behavioral sensitization to amphetamine results from an uncoupling between noradrenergic and serotonergic neurons. Proc Natl Acad Sci U S A 103(19):7476–7481

Sanches M, Scott-Gurnell K, Patel A, Caetano SC, Zunta-Soares GB, Hatch JP et al (2014) Impulsivity in children and adolescents with mood disorders and unaffected offspring of bipolar parents. Compr Psychiatry 55(6):1337–1341

Schepis TS, McFetridge A, Chaplin TM, Sinha R, Krishnan-Sarin S (2011) A pilot examination of stress-related changes in impulsivity and risk taking as related to smoking status and cessation outcome in adolescents. Nicotine Tob Res 13(7):611–615

Schoffelmeer AN, DeVries TJ, Wardeh G, van de Ven H, Vanderschuren LJMJ (2002) Psychostimulant-induced behavioral sensitization depends on nicotinic receptor activation. J Neurosci 22:3269–3276

Scocco P, Toffol E, Pilotto E, Ricardo P, Pavon L How the psychiatrists of a mental health department managed their patients before an attempted suicide. Psychiatry Clin Neurosci 63:706–714

Seo D, Tsou KA, Ansell EB, Potenza MN, Sinha R (2014) Cumulative adversity sensitizes neural response to acute stress: association with health symptoms. Neuropsychopharmacology 39 (3):670–680

Simon TR, Swann AC, Powell KE, Potter LB, Kresnow M, O'Carroll PW (2001) Characteristics of impulsive suicide attempts and attempters. Suicide Life Threat Behav 32(suppl 1):49–59

Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, Heninger GR, Charney DS (1993) Abnormal noradrenergic function in posttraumatic stress disorder. Arch Gen Psychiatry 50(4):266–274

Suicides at the Golden Gate Bridge (1999) Wikipedia. https://en.wikipedia.org/wiki/Suicides_at_the_Golden_Gate_Bridge

Sun H, Green TA, Theobald DE, Birnbaum SG, Graham DL, Zeeb FD, Nestler EJ, Winstanley CA (2010) Yohimbine increases impulsivity through activation of cAMP response element binding in the orbitofrontal cortex. Biol Psychiatry 67(7):649–656

Suokas J, Suominen K, Isometsa E, Ostamo A, Lonnqvist J (2001) Long-term risk factors for suicide mortality after attempted suicide--findings of a 14-year follow-up study. Acta Psychiatr Scand 104(2):117–121

Swann AC, Koslow SH, Katz MM, Maas JW, Javaid J, Secunda SK, Robins E (1987) Lithium carbonate treatment of mania. Cerebrospinal fluid and urinary monoamine metabolites and treatment outcome. Arch Gen Psychiatry 44:345–354

Swann AC, Bjork JM, Moeller FG, Dougherty DM (2002) Two models of impulsivity: relationship to personality traits and psychopathology. Biol Psychiatry 51:988–994

Swann AC, Pazzaglia P, Nicholls A, Dougherty DM, Moeller FG (2003) Impulsivity and phase of illness in bipolar disorder. J Affect Disord 73(1–2):105–111

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG (2004) Impulsivity: a link between bipolar disorder and substance abuse. Bipolar Disord 6:204–212

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG (2005a) Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. Am J Psychiatr 162(9):1680–1687

Swann AC, Birnbaum D, Jagar AA, Dougherty DM, Moeller FG (2005b) Acute yohimbine increases laboratory-measured impulsivity in normal subjects. Biol Psychiatry 57 (10):1209–1211

Swann AC, Moeller FG, Steinberg JL, Schneider L, Barratt ES, Dougherty DM (2007) Manic symptoms and impulsivity during bipolar depressive episodes. Bipolar Disord 9(3):206–212

Swann AC, Steinberg JL, Lijffijt M, Moeller FG (2008) Impulsivity: differential relationship to depression and mania in bipolar disorder. J Affect Disord 106(3):241–248

Swann AC, Steinberg JL, Lijffijt M, Moeller GF (2009a) Continuum of depressive and manic mixed states in patients with bipolar disorder: quantitative measurement and clinical features. World Psychiatry 8(3):166–172

Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG (2009b) Severity of bipolar disorder is associated with impairment of response inhibition. J Affect Disord 116(1–2):30–36

Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG (2011) Interacting mechanisms of impulsivity in bipolar disorder and antisocial personality disorder. J Psychiatr Res 45 (11):1477–1482

Swann AC, Lijffijt M, Lane SD, Cox B, Steinberg JL, Moeller FG (2013a) Norepinephrine and impulsivity: effects of acute yohimbine. Psychopharmacology 229(1):83–94

Swann AC, Lijffijt M, Lane SD, Steinberg JL, Acas MD, Cox B, Moeller FG (2013b) Pre-attentive information processing and impulsivity in bipolar disorder. J Psychiatry Res 47:1917–1924

Swick D, Honzel N, Larsen J, Ashley V, Justus V (2012) Impaired response inhibition in Veterans with post-traumatic stress disorder and mild traumatic brain injury. J Int Neuropsychol Soc 18:917–926

Takahashi T, Oono H, Inoue T, Boku S, Kako Y, Kitaichi Y, Kusumi I, Masui T, Nakagawa S, Suzuki K et al (2008) Depressive patients are more impulsive and inconsistent in intertemporal choice behavior for monetary gain and loss than healthy subjects--an analysis based on Tsallis' statistics. Neuro Endocrinol Lett 29(3):351–358

Voltaire, "Cato," Philosophical Dictionary (1764) In: Morley J (ed) The works of voltaire, a contemporary version, vol 7. E.R. DuMont, p 21, 1901

Witte TK, Merrill KA, Stellrecht NE, Bernert RA, Hollar DL, Schatschneider C, Joiner TE Jr (2008) "Impulsive" youth suicide attempters are not necessarily all that impulsive. J Affect Disord 107:107–116

Wolfe ME (1998) The role of excitatory amino acids in behavioral sensitization to stimulants. Prog Neurobiol 54:699–720

Yang PB, Swann AC, Dafny N (2003) Chronic pretreatment with methylphenidate induces cross-sensitization with amphetamine. Life Sci 73(22):289–2911

Zhang S, Hu HS, Hu J, Wu P-L, Chao HH, Li C-SR (2015) Barratt impulsivity and neural regulation of physiological arousal. PLoS One 10(6):e0129139

The Role of Impulsivity Facets on the Incidence and Development of Alcohol Use Disorders

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Contents

Abstract Alcohol Use Disorder (AUD) is a chronic relapsing disorder defined according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5; American Psychiatric Association 2013), "by a cluster of behavioural and physical symptoms, which can include, withdrawal, tolerance and craving". Social, emotional, behavioural and cognitive factors are important contributors to AUD. Impulsivity, a multifaceted behavioural concept, defined as a predisposition for rapid and unplanned actions, without considering potential negative consequences of these actions, represents an important such factor. In this chapter, research on the role of distinct impulsivity dimensions in different severity stages of alcohol use is presented.

Increased self-reported (trait) impulsivity and an inability to wait, as well as difficulty to adjust behaviour appropriately following a failure to withhold a

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response are observed across the spectrum of alcohol-use severities. Research on temporal impulsivity (inability to delay gratification) consistently shows deficits in more severe alcohol users. Data on temporal impulsivity in early stages of alcohol use are less consistent, with some studies showing no differences between high and moderate drinkers, while others indicating increased impulsivity in high alcohol users. Data on reflexion impulsivity are currently limited to draw conclusions. Recent research is also presented suggesting the importance of perception and interpretation of physiological and emotional signals on alcohol use behaviour highlighting the necessity of comprehensive integration of the field of the study of emotion and interoception with impulsivity research.

Keywords Binge drinking · Delay discounting · Emotion · Motor impulsivity · Risk taking

1 Introduction

Alcohol use disorder is a chronic relapsing disorder characterised by compulsive drinking, which denotes ongoing use of *alcohol* despite its negative consequences. According to the *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5; American Psychiatric Association 2013), alcohol use disorder (AUD) is defined "by a cluster of behavioural and physical symptoms, which can include withdrawal, tolerance and craving". The presence of these symptoms and their intensity are related to the severity of the disorder. Severity is based on the number of diagnostic criteria out of 11 listed in the DSM-5 but also on the frequency of alcohol drinking (e.g. days of drinking per week) and/or on the amounts of alcohol drunk (e.g. number of standard drinks per day), using self-reports of the individual. While craving (representing a strong motivational urge to drink) can be present during the early stages of the disorder, withdrawal is more often present at severe later stages of the disorder. Of additional concern are the patterns of drinking, with some being potentially more harmful than others. For example, measures of binge drinking, a pattern of alcohol use in which short periods of heavy alcohol consumption are intermixed with periods of abstinence (Townshend and Duka 2002; Lannoy et al. 2017b), may provide better prediction of potential dependency on alcohol. Binge drinking is associated with cognitive and emotional deficits, which may, in turn, lead further to harmful drinking (for review see Herman and Duka 2018).

Several factors, including social, emotional, behavioural and cognitive, as well as personality traits, have been identified as associates of heavy and/or risky alcohol drinking. Among personality traits, impulsivity, which is characterised by dysfunction in certain cognitive, behavioural as well as emotional domains, represents an important aspect associated with alcohol use, abuse and dependence (Dick et al. 2010; Lejuez et al. 2010; Potenza and de Wit 2010).

The understanding of the role of impulsivity in alcohol use and misuse has been hindered by several factors. Firstly, due to the variety of assessment methods, the concepts related to alcohol use severity have been difficult to unify. Secondly, the definition of a standard drink or unit of alcohol (i.e. ethanol grams in a standard drink or unit) is variable across different countries (Kalinowski and Humphreys 2016), which makes it problematic to directly compare research conducted across various institutions. Thirdly, binge drinking itself is not a unitary construct as binge drinkers can be characterised by distinct clusters associated with discrete psychological characteristics and alcohol consumption patterns (e.g. Gierski et al. 2017; Lannoy et al. 2017a). Finally, impulsivity itself is a multifaceted and multidimensional concept (Evenden 1999a; Caswell et al. 2015a; Herman et al. 2018a; Fig. 1), and its contribution to drinking, therefore, must be complex. To fully understand the role impulsivity plays in the incidence and development of AUD, the variety of facets of impulsivity should be considered.

This chapter summarises and discusses recent research and aims to provide up-to-date knowledge of the relationship between impulsivity and AUD. Importantly, impulsivity is thought to be both a determinant of drug use as well as a consequence of compulsive drug-seeking or intermittent alcohol drinking (e.g. Stephens and Duka 2008; de Wit 2009). However, the differentiation of impulsivity as a cause and effect of alcohol use is outside the scope of this review, and we refer the reader to a recent publication on the matter (Herman and Duka 2018). The current chapter will analyse

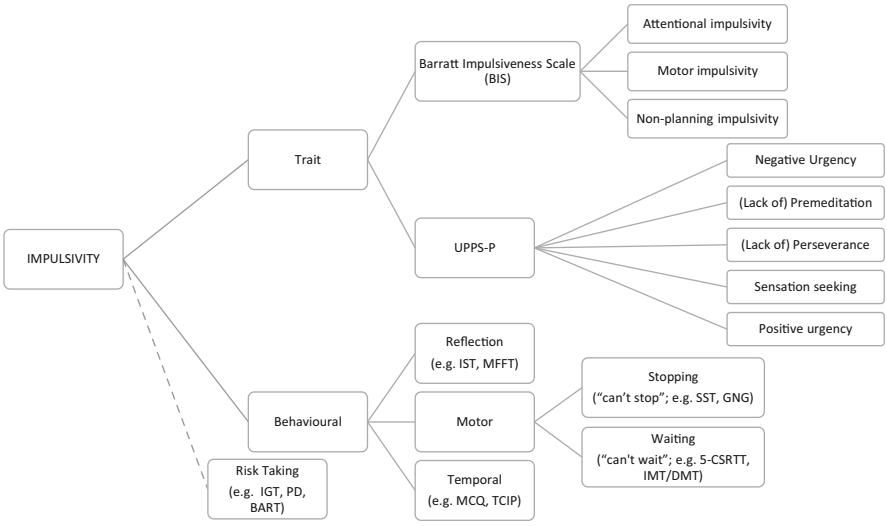

Fig. 1 Dimensions of impulsivity construct. *IST* information sampling task, *MFFT* matching familiar figures test, *SST* stop signal task, *GNG* go/no-go task, *5CSRTT* 5-choice serial reaction time task, *IMT/DMT* immediate/delay memory task, *MCQ* monetary choice questionnaire, *TCIP* two-choice impulsivity paradigm, *IGT* Iowa gambling task, *PD* probability discounting task, *BART* balloon analogue risk task. Note: Risk-taking is a concept related to impulsivity; however, it is often considered to be a separate construct

the relationship of impulsivity facets to emotional states and characteristics of alcohol use, including both severity and pattern of drinking.

2 Defining and Characterising Impulsivity in Humans

Broadly, impulsivity is a stable personality trait and/or behavioural marker of decision-making defined as a predisposition for rapid, unplanned actions, without considering potential negative consequences of these actions (Moeller et al. 2001). It encompasses a range of behaviours such as disinhibited thoughts and actions, difficulty sustaining attention or delaying gratification (Dalley and Robbins 2017). Distinct aspects of impulsivity are likely to be derived from different neural systems that are, at least partially, independent (Bari and Robbins 2013; Caswell et al. 2015a; Dalley and Robbins 2017; Herman and Duka 2018). Impulsivity mainly consists of trait characteristics measured using self-report questionnaires which assess general tendencies to impulsive actions in everyday situations and behavioural dimensions measured by various tasks in the present moment.

The Barratt Impulsiveness Scale (BIS; Patton et al. 1995) is one of the most frequently used measures of trait impulsivity. BIS distinguishes three distinct impulsivity facets: attentional (a lack of focus on the ongoing task), motor (acting without thinking) and non-planning impulsivity (orientation to the present rather than to the future). The UPPS-P Impulsive Behaviour Scale (Whiteside and Lynam 2001; Cyders and Smith 2007) is a more recent and increasingly popular measure. UPPS-P defines five separate subtypes of impulsive behaviours including aspects of emotional impulsivity.

Concerning behavioural impulsivity we describe a division into three dimensions depending on the stage at which behavioural output is affected by impulsivity, namely, reflection impulsivity (impulsive action preparation), motor impulsivity (impulsive action execution) and temporal impulsivity (impulsivity at the action-outcome stage) (Evenden 1999b; Caswell et al. 2015a). Figure 1 summarises the key information about the different subtypes of impulsivity construct.

Reflection impulsivity is characterised by a tendency to make fast decisions without adequate accumulation and evaluation of information (Kagan et al. 1964; Kagan 1965). It is assessed with tasks which measure the amount of information gathered before reaching a decision. Most commonly used tasks include the Information Sampling Task (IST; Clark et al. 2006) and the Matching Familiar Figures Test (MFFT; Cairns and Cammock 1978).

Motor impulsivity refers to an inappropriate execution of motor actions. It can be further divided into two subtypes. "Stopping" or "can't stop" impulsivity describes difficulty cancelling a motor response which is no longer appropriate. Common measures are the stop signal task (SST; Logan 1994) or Go/No-Go task (GNG; Hogg et al. 1975). The second subtype of motor impulsivity, "waiting" or "can't wait" impulsivity, reflects an inability to wait for an appropriate signal to act (Dalley et al. 2011; Robinson et al. 2009). It can be assessed with the Immediate and Delayed

Memory Task (IMT, DMT; Dougherty et al. 2002) or the 5-choice serial reaction time task (5-CSRTT; Sanchez-Roige et al. 2014; Voon et al. 2014).

Temporal impulsivity indicates the difficulty in awaiting gratification. Although the subjective value of a reward generally decreases as a function of a delay to its delivery (delay discounting, DD; Van Den Bos and McClure 2013), impulsive individuals tend to discount delay rewards more steeply (Ainslie 1975; Kirby et al. 1999). Temporal impulsivity in humans can be assessed with hypothetical choice procedures (e.g. monetary choice questionnaire, MCQ; Kirby et al. 1999). Alternatively, behavioural paradigms such as two choice impulsivity paradigm (TCIP; Dougherty et al. 2005) can be used to assess real decisions during which participants experience a delay between their choice and a reward delivery.

Another concept related to impulsivity is a *tendency to take risks*. Notably, risk-taking is considered to be an integral part of impulsivity construct by some (e.g. Zuckerman et al. 1978; Whiteside and Lynam 2001; de Wit 2009; Fineberg et al. 2010, 2014; Winstanley et al. 2010), while others consider risk-taking to be separate from impulsivity (Patton et al. 1995; Caswell et al. 2015a; also see Herman et al. 2018b for discussion). Recent evidence from the principal component analysis in a large sample of young adults ($N > 500$) provides evidence that measures of risk-taking (both trait and behavioural) and impulsivity are dissociable from each other (Herman et al. 2018b). This dissociation is further exemplified by the relationship with emotional state: measures of risk-taking tend to be associated with enhanced positive emotional states, while measures of impulsivity are related to enhanced negative emotional states (Herman et al. 2018b). Importantly risky behaviours are often investigated for their relationship with alcohol use and misuse.

The UPPS-P sensation-seeking subscale can be used to asses risk-taking as a personality trait (Herman et al. 2018b). Behaviourally, risk-taking can be assessed with various gambling-like paradigms or questionnaires, such as probability discounting questionnaire (Madden et al. 2009), Iowa gambling task (IGT) (Bechara et al. 1994), or the balloon analogue risk task (BART) (Lejuez et al. 2002).

3 Alcohol Use and the Facets of Impulsivity

Alcohol use is characterised by heterogeneity, including in the patterns of drinking. "Binge drinkers" (BD) engage in a particularly deleterious pattern of drinking, resulting in marked changes in brain structures and behavioural and emotional deficits (e.g. Stephens and Duka 2008; Smith et al. 2017; Herman and Duka 2018). Alcohol use population is further characterised by facets of personality including impulsive traits (e.g. Jones et al. 2014; Caswell et al. 2015b; Sanchez-Roige et al. 2016; Gierski et al. 2017).

According to the Temperament and Character Inventory (TCI; Cloninger et al. 1993, 1994), the personality characteristics of alcohol-dependent individuals support them being divided into two groups, Type I and Type II (Cloninger et al. 1996). TCI provides four dimensions of temperament trait (novelty seeking, harm avoidance,

reward dependence and persistence) and three dimensions of character trait (self-directedness, cooperativeness and self-transcendence). Type I, more common in females, is characterised by low novelty seeking and high harm avoidance, as well as by initiation of drinking later in life and a coping motive. Type II, more common in males, is characterised by high scores of novelty seeking and low scores of harm avoidance, an earlier onset of heavy drinking and a stronger genetic influence. Type II alcohol-dependent individuals tend to exhibit more impulsive traits than do Type I and report drinking in order to experience euphoria. Recent studies have added further information on these two distinct alcohol dependency subgroups supporting further the notion that Type I and Type II are associated with distinct biological determinants and markers according to gender and personality trait (Kärkkäinen et al. 2013; Laukkanen et al. 2015a, b; Gierski et al. 2017). Gierski et al. (2017) have demonstrated that among BD, two distinct subgroups could be identified differing in the composition of gender and reflecting personality and drinking characteristics of Type I and Type II. In post-mortem autoradiography studies, Type I drinkers have shown decreased opiate binding in brain areas associated with memory and mood disorders compared to controls, and Type II have shown increased glutamatergic binding in areas associated with impulse control and decision-making compared to Type I drinkers (Kärkkäinen et al. 2013; Laukkanen et al. 2015a, b).

Taken together the findings presented in this section, it becomes apparent that there are specific behavioural and biological factors that associate with the subgroups of alcohol dependence, and that there is a need for an understanding of AUD heterogeneity. Although impulsive trait has been clearly associated with Type II alcohol dependence and not with Type I, research in the relationship between these two subgroups and the facets of impulsivity is limited (Bjork et al. 2004; Gierski et al. 2017) and found higher self-ratings of impulsivity (as measured with BIS) and increased behavioural impulsivity (as measured by increased commission errors in a memory task) in Type II compared to Type I individuals.

3.1 Trait Impulsivity and Alcohol Use

There is a large body of research showing a positive association between trait impulsivity (evaluated by either BIS or UPPS-P or both) and alcohol consumption, including harmful and problematic drinking (e.g. Fox et al. 2010; Adams et al. 2012; Hamilton et al. 2012; Coskunpinar et al. 2013; Stautz and Cooper 2013; Jakubczyk et al. 2013). For example, BIS and UPPS-P ratings were associated with AUDIT measures of hazardous drinking in a community sample of social drinkers (Fox et al. 2010; MacKillop et al. 2016). Moreover, heavy-drinking university students showed increased self-reported non-planning and motor impulsivity (BIS subscales) compared to those who did not exceed drinking guidelines (Papachristou et al. 2012; Caswell et al. 2015b). Similar findings have been observed when binge drinking

ratings were taken into account: BD showed increased trait impulsivity as measured by BIS compared to non-BD (Moreno et al. 2012; Sanchez-Roige et al. 2014). Emotional aspects of impulsivity, particularly negative urgency (measured by UPPS-P), also seem to predict binge drinking score after controlling for gender and age (Bø et al. 2016b), suggesting that negative emotional states may enhance excessive drinking in vulnerable individuals. A more recent study investigated UPPS-P ratings of impulsivity with respect to separate alcohol-related outcomes finding that while positive and negative urgency subscales were associated with alcohol-related problems, lack of premeditation was associated with alcohol intake and binge drinking (Tran et al. 2018). An earlier large-scale study on a student population showed that negative urgency, lack of premeditation, and sensation-seeking subscales bore significant, positive relationship with problem drinking (Adams et al. 2012). Further efforts to estimate the contribution of UPPS-P subscales to alcohol dependency problems separately have indicated that negative urgency is more related to problems experienced during a drinking episode, whereas positive urgency is associated with alcohol problems that result from long-term drinking tendencies (McCarty et al. 2017). Moreover, evidence from a large study suggests that at earlier stages of alcohol use, trait impulsivity can predict alcohol use patterns. For example, Wardell et al. (2016) tested 300 young adults (18–25 years old) reporting at least one heavy-drinking episode in the past month, on their ratings on UPPS-P and BIS scales. The lack of perseverance and lack of premeditation scales of the UPPS-P and all subscales of the BIS-11 predicted unique variance in heavy-drinking frequency, while the emotional (positive and negative urgency scales of the UPPS-P) and the attention impulsivity subscale of the BIS-11 predicted unique variance in self-reported impaired control and alcohol problems.

Interestingly, a recent review (Um et al. 2019) argued for convergence between areas of the brain related to addiction cycle (orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex and amygdala) and emotional processing and those related to impulsivity, as measured by self-ratings of negative urgency. Herman et al. (2018a) have also suggested that emotional processing-related structures show convergence with brain areas involved in impulsive behaviours.

The focus in recent literature on trait impulsivity, as measured with UPPS-P, and alcohol-related problems may indicate the need to direct research towards aspects of emotional processing and impulsivity (see Sect. 3.4 for a more detailed discussion on this matter). In conclusion, although self-reported impulsivity seems to be high in heavy and binge drinkers, as discussed here, there is little consensus on how the particular subtypes (subscales) of trait impulsivity are specifically related to heavy alcohol consumption. Overall, it seems that higher trait impulsivity levels more generally might be associated with heavy use. We have summarised the findings regarding distinct subtypes of trait impulsivity with relation to alcohol use problems in Table 1.

Table 1 Summary of studies that showed increased trait impulsivity domains among different alcohol users' subdomains

Trait impulsivity domain	Social drinkers	Binge drinkers	Problem/hazardous/AUD
BIS non-planning	Fox et al. (2010)[a]; Papachristou et al. (2012)[b]; Caswell et al. (2015b)[c]; MacKillop et al. (2016)[d]	Moreno et al. (2012)[b]	Hamilton et al. (2012)[a]; Coskunpinar et al. (2013)[d]; Jakubczyk et al. (2013)[e]
BIS attention	Fox et al. (2010)[a]; MacKillop et al. (2016)[d]		Hamilton et al. (2012)[a]; Jakubczyk et al. (2013)[e]; Wardell et al. (2016)[c]
BIS motor	Fox et al. (2010)[a]; Papachristou et al. (2012)[b]; Caswell et al. (2015b)[c]; MacKillop et al. (2016)[d]	Moreno et al. (2012)[b]; Sanchez-Roige et al. (2014)[b]	Hamilton et al. (2012)[a]; Jakubczyk et al. (2013)[e]
UPPS-P negative urgency	Curcio and George (2011)[c]; MacKillop et al. (2016)[d]	Bø et al. (2016) b[c]	Adams et al. (2012)[c]; Coskunpinar et al. (2013)[d]; Stautz and Cooper (2013)[d]; Wardell et al. (2016)[c]; McCarty et al. (2017)[a]; Tran et al. (2018)[c]
UPPS-P (LACK OF) perseverance	Coskunpinar et al. (2013)[d]; MacKillop et al. (2016)[d]; Wardell et al. (2016)[c]		
UPPS-P (LACK OF) premeditation	MacKillop et al. (2016)[d]; Wardell et al. (2016)[c]	Tran et al. (2018)[c]	Adams et al. (2012)[c]
UPPS-P sensation seeking	Curcio and George (2011)[c]; Stautz and Cooper (2013)[d]		Adams et al. (2012)[c]
UPPS-P positive urgency	Curcio and George (2011)[c]; Stautz and Cooper (2013)[d]; MacKillop et al. (2016)[d]		Coskunpinar et al. (2013)[d]; Stautz and Cooper (2013)[d]; Wardell et al. (2016)[c]; McCarty et al. (2017)[a]; Tran et al. (2018)[c]

[a]Correlational analyses to determine factors contributing to alcohol consumption in heavy drinkers from local communities
[b]Comparisons heavy vs light or binge drinkers vs non-binge drinkers or problem drinkers versus nonproblem drinkers among social drinkers
[c]Correlational analyses to determine factors contributing to alcohol abuse in social drinkers among college students
[d]Meta-analyses studies
[e]Correlational analyses to determine severity in AUDs
[f]Studies on adolescents

3.2 Behavioural Impulsivity and Alcohol Use

Facets of behavioural impulsivity have been examined with the use of several tasks, the most common of those described above (Sect. 2). An important consideration that is sometimes overlooked in impulsivity research is small or null correlations between self-reported and behavioural impulsivity measures, suggesting that these outcomes measure distinct, non-covarying processes (e.g. Clark et al. 2006; Broos et al. 2012; Caswell et al. 2015a).

3.2.1 Reflection Impulsivity and Alcohol Use

Research on reflection impulsivity and alcohol use provides mixed results. For example, Caswell et al. (2015b) found no differences in performance on the IST between university students exceeding UK alcohol use guidelines and those that did not. Similarly, Banca et al. (2016) reported that BD were no different from non-BD on the IST. It is worth noting that the same study also employed another task, the beads task, used as a measure of jumping to conclusions. Interestingly, in this task, BD accumulated less information before making a decision, compared to non-BD, suggesting that the beads task may be more sensitive in detecting deficits in reflection impulsivity in BD. In contrast to the studies described above, Townshend et al. (2014) showed that BD exhibited more impulsive behaviour on the IST than non-BD: BD gathered less information before making a decision and committed more errors. Similarly, alcohol-dependent individuals have been reported to sample less information than healthy controls before deciding on the IST, showing increased reflection impulsivity (Lawrence et al. 2009a). A longitudinal study (baseline and follow-up 18 months later) on university students also found that future severity of binge drinking was uniquely predicted by performance on the IST, and not on the SST or the Iowa gambling task (Bø et al. 2017).

The inconsistent results with regard to reflection impulsivity and the introduction of a new reflection impulsivity task, which may be more sensitive in detecting deficits in BD, indicate a need for further research. Possibly, the differences in reflection impulsivity as measured in the IST arise at later stages of alcohol use severity.

3.2.2 Motor Impulsivity

Waiting Impulsivity

Research on motor ("can't wait") impulsivity is somewhat limited in humans. However, recent studies have found that young adult BD not yet presenting AUD (Sanchez-Roige et al. 2014; Morris et al. 2016) show increased premature responding in the 5-CSRTT compared to non-BD. This suggests that BD, who are

more at risk to develop subsequently alcohol-related problems and AUD, exhibit difficulty with waiting to produce an accurate response. Such an increase in premature responding was replicated in animal models, specifically in two mice strains, one prone to alcohol drinking and one that is not, suggesting that waiting impulsivity might represent an endophenotype for AUD (Sanchez-Roige et al. 2014). This proposal was further supported by the finding that among young social drinkers with equal binge drinking propensity, those with familial history of AUD showed high premature responses compared to those without a familial history. Along those lines, abstinent alcohol-dependent individuals (Voon et al. 2014) make increased numbers of premature responses on the 5-CSRTT.

Stopping Impulsivity

While elevated "stopping" motor impulsivity is observed in individuals with alcohol dependence (e.g. Goudriaan et al. 2006), a number of studies comparing either heavy with light social drinkers or BD with non-BD show no differences in motor response inhibition (López-Caneda et al. 2012; Moreno et al. 2012; Wetherill et al. 2013b; Sanchez-Roige et al. 2014; Caswell et al. 2015b; MacKillop et al. 2016; Worhunsky et al. 2016). However, heavy social drinkers do show difficulty adjusting behavioural responses on the SST. For example, while low drinkers typically slow their response times after an incorrect response on a stop trial, heavy drinkers fail to do so (Caswell et al. 2015b); this is despite there being no group differences found for the primary measures of stopping impulsivity. Similarly, Bø et al. (2016a) reported a similar pattern of results when comparing BD and non-BD. It is possible that binge-drinking and heavy alcohol use are not associated with increased "stopping impulsivity" per se but rather with disrupted behavioural adjustment mechanisms. Taken these data together, it could be suggested that inability to stop a prepotent response may only arise in later stages of AUD.

Despite the limited behavioural evidence for stopping impulsivity deficits in BD or heavy-drinking, non-dependent subjects, *neuroimaging findings*, indicate that successful response inhibition may be related to significantly higher activation of the right inferior frontal cortex, a region of the brain known to be involved in inhibitory control (Aron et al. 2014), in BD. This finding suggests that BD may need to recruit more neural resources for successful implementation of inhibition than controls do (López-Caneda et al. 2012), leading to no differences at the behavioural level. A recent imaging study (Herman et al. 2019a) using the SST also found that binge drinking score was associated with elevated activation in brain structures related to inhibitory control (frontal pole) during successful inhibition, providing further support to the idea that light alcohol consumption in young adults is related to compensatory recruitment necessary for motor inhibition implementation (López-Caneda et al. 2012; Hatchard et al. 2017).

These altered neural mechanisms may, to some extent, anticipate and predict later patterns of hazardous alcohol use. In adolescents and young adults, an escalating drinking trajectory was prospectively associated with altered frontoparietal control

mechanisms during GNG and SST performance (Whelan et al. 2012; Wetherill et al. 2013b; Worhunsky et al. 2016). Future heavy drinkers showed less activation of inhibitory circuitry than control subjects before the onset of heavy drinking, but after transitioning into heavy drinking, they showed more activation during response inhibition than nondrinking controls (Wetherill et al. 2013b). In addition, substance-naïve adolescents who would later go on to experience alcohol-induced blackouts show increased neural activity in frontal and cerebellar brain regions during inhibitory processing, as compared to adolescents who go on to drink at similar levels but do not experience blackouts and to healthy, nondrinking controls, suggesting a neurobiological vulnerability to alcohol-induced memory impairments (Wetherill et al. 2013a). In young (18–21 years old) social drinkers, regression analyses revealed that both trait impulsivity assessed with BIS and inhibitory failures on the GNG task correlated with quantity and frequency of drinking over the past month. However, only the inhibitory failures on the GNG task, and not the impulsivity questionnaire scores, correlated with the largest number of drinks consumed on one occasion during the past month (Henges and Marczinski 2012).

The presentation of stimuli with emotional or affective value may influence the ability to stop an initiated response and associated neural activation patterns in alcohol users. We used a variant of the SST task in which go and stop stimuli were presented within a context of fearful or neutral images, finding young adult BD exhibited better response inhibition in the fearful vs neutral condition (Herman et al. 2019a). Additionally, we found greater activation in frontal areas during successful response inhibition, regardless of the emotional context, was associated with the intensity of binge drinking (again suggesting a compensatory mechanism). However, within the fearful relative to neutral context, higher binge drinking was related to attenuated frontal and parietal activation. Such a finding indicates the selective emotional facilitation of inhibitory control (Herman et al. 2019a). Interestingly, similar neuroimaging findings were observed in college-aged BD using an emotional GNG task (Cohen-Gilbert et al. 2017); a higher recent incidence of binge drinking was significantly associated with decreased activation of prefrontal regions strongly implicated in executive functioning, during negative, relative to neutral, inhibitory trials.

The altered inhibitory control-related neural activity may also extend to conditions in which alcohol cues are present. For example, heavy drinkers show increased prefrontal, insula and cingulate activation and poorer behavioural response inhibition, on the GNG task when alcohol-related stimuli are presented (Ames et al. 2014). Using a flanker task, alcohol-related stimuli (versus neutral stimuli) exacerbated the interference associated with incongruent stimuli, and this flanker effect was positively correlated with the participants' average weekly alcohol intake (Nikolaou et al. 2013).

Together, the evidence suggests that response-inhibition mechanisms are affected in heavy alcohol users. Such deficits are reflected in disrupted behavioural adjustments and with affected activity within the frontoparietal control network during motor response inhibition. Importantly, these mechanisms may be further altered in the presence of salient emotional stimuli, including alcohol-related cues.

3.2.3 Temporal Impulsivity

Numerous studies have shown elevated delay discounting (i.e. increased temporal impulsivity) in individuals presenting higher levels of alcohol abuse and dependence (MacKillop et al. 2011; Gerst et al. 2017; Bernhardt et al. 2017). Steeper discounting of delayed rewards (higher temporal impulsivity) has been associated with an earlier onset of AUD symptoms (Dom et al. 2006) and has been identified as a predictor for relapse following treatment for a range of substances (e.g. Sheffer et al. 2014; Stevens et al. 2015). Moreover, discounting rates are significantly correlated with the severity of drinking and with associated problems caused by drinking, whereby higher amounts of alcohol drunk and more alcohol-related problems are associated with the higher temporal discounting (Petry 2001; Mitchell et al. 2005; Claus et al. 2011; MacKillop et al. 2011; Courtney et al. 2012).

Data on the temporal impulsivity in social drinkers are more equivocal. While some studies reported no differences in temporal impulsivity between BD (Banca et al. 2016) or heavy social drinkers (Caswell et al. 2015b) and their low-drinking counterparts, others do (Moreno et al. 2012; Sanchez-Roige et al. 2014). Vuchinich and Simpson (1998) also reported that heavy social drinkers, as well as problem drinkers, show greater delay discounting compared to light social drinkers; this relationship was stronger for problem drinkers, suggesting that the amount and frequency of alcohol consumption may be a crucial factor. A recent study (Bailey et al. 2019) with problematic alcohol users, in which also IQ was measured, has also shown that higher temporal impulsivity was associated with more lifetime alcohol problems (as shown previously Courtney et al. 2012), more recent alcohol use and lower IQ. Additionally, a study looking at delayed discounting among social drinkers for alcohol and monetary rewards found that heavier drinkers showed higher temporal impulsivity for both monetary and alcohol rewards compared with lighter drinkers (Adams et al. 2017). In addition, O'Halloran et al. (2018) reported BIS attentional and non-planning impulsivity as well as temporal, but not other impulsivity, domains predict intoxication frequency in young adult social drinkers.

Despite the associations described above, temporal impulsivity may not as readily predict alcohol use progression. For example, though delay discounting was associated with baseline alcohol use in a group of 18-year-old males, it did not predict the drinking trajectories over the following 12 months (Bernhardt et al. 2017). Similarly, delay discounting did not longitudinally predict the frequency of intoxication episodes or the development of alcohol problems in early adolescents followed for 2 years (Fernández-Artamendi et al. 2018). Further support for these proposals also comes from a recent study in which patients with AUD showed higher rates of delayed discounting compared to controls; while no evidence for a relationship between delayed discounting and severity of alcohol consumption was found, the increased rates of delayed discounting in AUD were found irrespective of the presence of comorbid psychopathology (Gowin et al. 2019).

Research using *neuroimaging* techniques indicates that, when choosing a delayed over an immediate reward, individuals with more severe drinking problems, compared to individuals with fewer problems, show a greater activation in several key

brain regions involved in response inhibition and interoceptive processing, including the right inferior frontal gyrus, supplementary motor and insula (Claus et al. 2011). Similarly, individuals with AUD show over-activation in the ventromedial prefrontal cortex (an area supporting decision-making processes) when choosing delayed over immediate rewards, a result that is positively associated with alcohol dependence severity (Lim et al. 2017).

Taking these findings together, it seems that problem drinkers and alcohol-dependent individuals require greater effort to overcome their immediate bias. Interestingly, in emotional context, when young adult BD were tested on an affective version of the MCQ, during which monetary-delay questions are presented with fearful and neutral task-irrelevant stimuli (Herman et al. 2019a), frontal pole activation was negatively correlated with binge scores when individuals made a delayed over immediate choice in the fearful vs neutral context. These results corroborate with our findings from the affective SST (see above), in that negative emotional context seems to require less neural resources in individuals who binge-drink more, suggesting that in more arousing contexts, BD may perform more efficiently.

Together, the findings presented here suggest that elevated temporal impulsivity might be a characteristic feature of problematic alcohol use and may not be affected in light social drinkers or early in life BD, thus suggesting that temporal impulsivity might be one of the characteristics of AUD which develops with the progression of the disease.

3.3 Risk-Taking

Though risk-taking tendencies may not be a key manifestation of impulsivity (Herman et al. 2018a, b, 2019a), it is often considered to be a part of a multidimensional impulsivity construct.

Risky behaviours can be associated with high novelty seeking, a factor suggested being a predictor of drug or alcohol abuse. Although such a relationship with novelty seeking seems to be important in understanding the role of risk-taking in AUD development, studies have mostly examined the role of novelty seeking and risk-taking in alcohol abuse independently. Possibly, this factor may explain why findings regarding the relationship between alcohol drinking severity and risk-taking are mixed, particularly in studies of young social drinkers. In student populations, trait sensation seeking, equivalent to trait novelty seeking, typically is not predictive of alcohol-related problems (Cooper et al. 1995; Magid et al. 2007; Cyders et al. 2009; Curcio and George 2011), though it is correlated with alcohol consumption quantities and frequencies (Del Boca et al. 2004; Curcio and George 2011). However, sex differences may play a moderating role. A study looking at alcohol use within a large sample of university students reported that the odds of being a BD vs non-BD increased as risk-taking tendencies increased for both men and women (de Haan et al. 2015), while the odds of being a non-binge drinker versus abstinent were increased as a function of risk-taking for women only.

Regarding behavioural risk-taking tendencies, performance on the BART, together with high ratings of BIS non-planning impulsivity but not temporal or motor "stopping" impulsivity, predicted alcohol use in a group of university students (Fernie et al. 2010). Interestingly, in a community sample of individuals with or without risk for AUD, those with higher symptom count made fewer pumps per trial on the BART, indicating less risk-taking (Ashenhurst et al. 2011). Importantly, IQ and age mediated the relationship between risk-taking propensity and symptom count, suggesting the importance of other factors in the relationship between risk-taking and alcohol use. Furthermore, probability discounting, both for gains and losses, as well as loss aversion measured at baseline in young social drinkers (18-year-old males) do not seem to be related to trajectories of alcohol use over a 12-month period (Bernhardt et al. 2017), suggesting that these type of risk-taking behavioural measures are less relevant as predisposing factors for alcohol consumption in young adults.

The data is more consistent in clinical samples. Detoxified AUD patients, compared to the control group, show lower risk aversion regarding probabilistic gains, lower risk-seeking regarding probabilistic losses and lower loss aversion facing mixed prospects. Furthermore, preference towards probabilistic over certain rewards at baseline was predictive of relapse in patients (Bernhardt et al. 2017). These results suggest that risk-taking behaviour may develop during the course of continuous alcohol use and that assessing risk-tendencies may be useful in identifying individuals vulnerable for release (Bernhardt et al. 2017). Further, recent meta-analyses (Kovács et al. 2017; Stephan et al. 2017) revealed that AUD patients show a decision-making deficit on the IGT compared to healthy controls, indicating that this deficit may contribute to poor therapeutic outcomes.

Therefore, the role of risk-taking at different stages of alcohol use trajectory is not straightforward, and other factors, such as demographics, IQ or novelty aspects during impulsive choices involving risk, should be taken into account for the evaluation of that relationship.

The findings summarised here present a complex picture of the role of distinct domains of behavioural impulsivity at different stages of alcohol use problems. To aid the reader in the interpretation of the findings, we summarize the results in Table 2.

3.4 Future Directions

Throughout the previous sections, we have sparingly mentioned the role of emotional impulsivity traits (positive and negative urgency) and impulsive actions within an emotional context (e.g. Cohen-Gilbert et al. 2017; Herman et al. 2019a) in alcohol use. Emotional state at initiation and continuation of alcohol use and dependence seems to be of importance, as negative emotional states, leading to alcohol use for relief, represent a crucial part of negative reinforcement models of addiction (e.g. Conger 1956; Cooper et al. 1995; Swendsen et al. 2000; Zack et al. 2002;

Table 2 Summary of literature discussed in the chapter regarding the behavioural impulsivity in alcohol use

Impulsivity domain	Increased ↑	Null results	Decreased ↓
Reflection	• BD (Townshend et al. 2014)[a] • AUD (Lawrence et al. 2009b)[b]	• Students exceeding UK guidelines and BD (Caswell et al. 2015b;[c] Banca et al. 2016)[c]	
Motor "can't wait"	• BD and abstinent AUD (Sanchez-Roige et al. 2014;[a] Voon et al. 2014;[b] Morris et al. 2016)[a]		
Motor "can't stop"	• AUD (Goudriaan et al. 2006)[b]	• BD and social drinkers (López-Caneda et al. 2012;[a] Moreno et al. 2012;[a] Wetherill et al. 2013b;[a, e] Sanchez-Roige et al. 2014;[a] Caswell et al. 2015b;[c] MacKillop et al. 2016;[d] Worhunsky et al. 2016)[a, e]	• In BD in the fearful vs neutral context (Herman et al. 2019a)[c]
Temporal	• Social drinkers (Vuchinich and Simpson 1998;[a] Moreno et al. 2012;[a] Sanchez-Roige et al. 2014;[a] Adams et al. 2017; O'Halloran et al. 2018)[c] • AUD and heavy drinkers (Petry 2001;[b] Mitchell et al. 2005;[b] Dom et al. 2006;[b] MacKillop et al. 2011;[d] Sheffer et al. 2014 *(in smokers)*; Stevens et al. 2015 *(in SUDs)*; Gerst et al. 2017;[b] Bernhardt et al. 2017)[a, b]	• BD and social drinkers (Caswell et al. 2015b;[c] Banca et al. 2016)[c]	
Risk-taking	• Social drinkers (Fernie et al. 2010)[c] • AUD (Kovács et al. 2017;[c] Stephan et al. 2017;[d] Bernhardt et al. 2017)[a, b]	• Social drinkers (Cooper et al. 1995;[c] Magid et al. 2007;[c] Cyders et al. 2009;[c] Curcio and George 2011)[c]	• Community sample at risk of AUD (Ashenhurst et al. 2011)[c]

[a]Comparisons heavy vs light or binge drinkers vs non-binge drinkers or problem drinkers versus nonproblem drinkers among social drinkers
[b]Comparisons AUDs vs HCs
[c]Correlational analyses to determine factors contributing to alcohol abuse in social drinkers among college students
[d]Meta-analyses studies
[e]Studies on adolescents

Simons et al. 2005, 2010; Peacock et al. 2015; Dvorak et al. 2016). Recently, the role of emotional states in modulating impulsivity and its contribution to alcohol and other drug use is found increasingly important (for a review see Herman and Duka 2018). In response to intense emotional arousal, rash actions can provide a distraction from distress caused by the emotional arousal (Cyders and Smith 2008). A comprehensive discussion of this field is beyond the scope of this chapter; however, since the research in this area is on the rise, it is important to highlight recent developments in the field and propose new directions.

Indulging in impulsive drinking to regulate one's mood state may be a strategy used particularly often by individuals presenting high trait or behavioural impulsivity levels (Cyders et al. 2010; Fox et al. 2010; Simons et al. 2010; Dinc and Cooper 2015; Anthenien et al. 2017). Importantly alcohol misuse is found to be associated with alexithymia, that is a general deficit in identifying and describing feelings in self and others (Taylor 2000; Taylor et al. 2003). Frequent intoxications and long-term heavy alcohol use are linked to alexithymia (Kauhanen et al. 1992). Recent research suggested that alexithymia, which results from impaired processing of bodily sensations (including physiological arousal), underpins the urge to consume alcohol in social drinkers (Betka et al. 2017). Moreover, an exciting new finding regards the association between accurate discrimination of internal (own heartbeat) from external signals (discrete repeated sounds of different heart rates; interoceptive accuracy) and non-planning impulsivity (Herman et al. 2019b), opening a novel avenue of interesting research which may lead to fresh therapeutic opportunities. Indeed, poor ability to sense bodily cues has been linked to craving in AUD patients, suggesting that those with poorer ability to accurately feel their heartbeat reported more the craving (Ateş Çöl et al. 2016). High interoceptive awareness was also found to positively associate with an increased subjective experience of alcohol-related effects in social drinkers (Leganes-Fonteneau et al. 2019) possibly reinforcing the action to consume alcohol again.

Together, these findings suggest that appropriate sensation of internal bodily state might be an adaptive mechanism guiding our actions and decision. It is reasonable then to suggest that when this mechanism does not function correctly, appropriate decision-making and evaluation of more long-term bodily changes, including those related to addiction, will be malfunctioning. For instance, poor ability to correctly identify bodily state may confuse interpretation of bodily sensations such as signals of hunger, arousal, proprioception, tiredness or temperature with affective states (i.e. misinterpret anger as heat, pain, hunger etc.; Brewer et al. 2016). This, of course, may lead to various negative consequences such as inappropriate actions due to misperceived sensations and ineffective management of arousal due to an inability to interpret it. Indeed, it has been suggested that interoceptive ability is vital for higher-order cognition and that atypical interoception may predispose to psychopathology, risky behaviour as well as poor emotional functioning or resilience to stressful situations (Haase et al. 2016; Murphy et al. 2017). Importantly, a dissociation between self-reported and objective measures of interoception was recently reported in alcohol abuse (Jakubczyk et al. 2019): AUD patients showed lower ability to accurately perceive physiological sensations (interoceptive accuracy) but presented

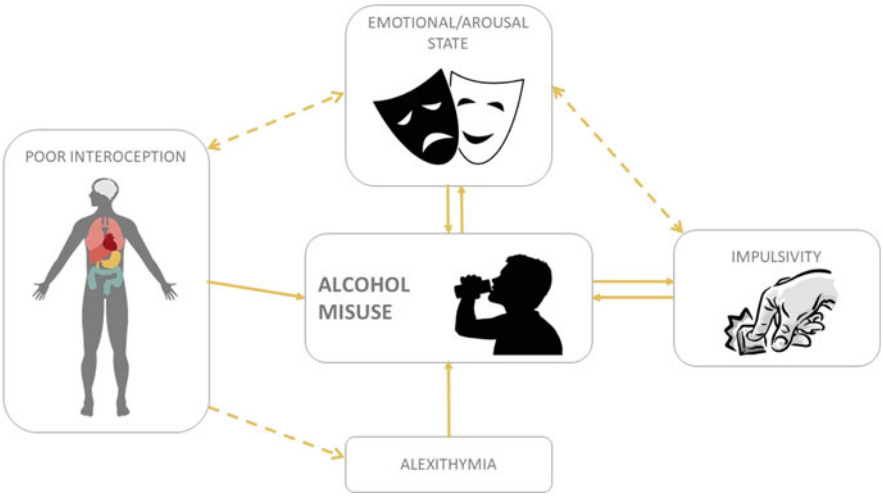

Fig. 2 Some of the factors, which directly (solid lines) or by association (dotted lines), influence alcohol use

enhanced perceived self-judgements of one's abilities (interoceptive sensibility). Targeting this "mismatch" between subjective judgement and objective ability to perceive one's physiological state in AUD could also be useful therapeutically in the future in prevention and treatment of alcohol abuse.

Together, the results summarised above suggest that individuals may engage in drinking alcohol to manage emotional states (particularly states of high arousal), which in turn modulate impulsivity and can be associated with poor interoception. Moreover, poor interoception and emotional dysregulation (alexithymia) affect alcohol misuse. Importantly, using alcohol as a coping strategy is most frequent in highly impulsive individuals. Figure 2 summarises these relationships. Future research should target the mutual relationship between the role of recognition and interpretation of one's own emotional and physiological state with distinct dimensions of impulsivity and their joint contribution to initiation and maintenance of alcohol use, specifically focusing on developing fresh therapeutic methods.

4 Conclusions

In this chapter, research on the role of distinct impulsivity dimensions and different stages of alcohol misuse is presented. Specifically, heavy and problematic alcohol use is associated with increased self-reported (trait) impulsivity and an inability to wait, as well as difficulty in adjusting behaviours appropriately following a failure to withhold a response. These impairments are observed across the spectrum of alcohol-use severities. Data regarding temporal and reflection impulsivity are less

consistent, with some studies showing no differences between high and moderate drinkers, while others indicating increased both types of impulsivities in high alcohol users. Regarding temporal impulsivity, research consistently shows difficulties in delay gratification in more severe alcohol users. This complex picture of impulsivity dimensions-alcohol use severity relationship calls for more longitudinal studies which would allow differentiating between the role of impulsivity as a predisposing factor and a cause of continuous alcohol use.

Moreover, recent research increasingly suggests the importance of perception and interpretation of physiological and emotional signals on alcohol use behaviour. The growing recognition of the importance of both, the emotional impulsivity in addiction field and the interaction between current physiological state and impulsivity, highlights the necessity of comprehensive integration of the field of the study of emotion and interoception with impulsivity research. We strongly believe that this comprehensive approach promises fresh therapeutic options for patients suffering from AUD but also for better prevention in at-risk populations.

References

Adams ZW, Kaiser AJ, Lynam DR et al (2012) Addictive behaviors drinking motives as mediators of the impulsivity-substance use relation: pathways for negative urgency, lack of premeditation, and sensation seeking. Addict Behav 37:848–855. https://doi.org/10.1016/j.addbeh.2012.03.016

Adams S, Attwood AS, Munafo MR (2017) Drinking status but not acute alcohol consumption influences delay discounting. Hum Psychopharmacol 32:e2617. https://doi.org/10.1002/hup.2617

Ainslie G (1975) Specious reward: a behavioral theory of impulsiveness and impulse control. Psychol Bull 82:463–496. https://doi.org/10.1037/h0076860

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Association, Washington

Ames SL, Wong SW, Bechara A et al (2014) Neural correlates of a Go/NoGo task with alcohol stimuli in light and heavy young drinkers. Behav Brain Res 274:382–389. https://doi.org/10.1016/j.bbr.2014.08.039

Anthenien AM, Lembo J, Neighbors C (2017) Drinking motives and alcohol outcome expectancies as mediators of the association between negative urgency and alcohol consumption. Addict Behav 66:101–107. https://doi.org/10.1016/j.addbeh.2016.11.009

Aron AR, Robbins TW, Poldrack RA (2014) Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci 18:177–185

Ashenhurst JR, Jentsch JD, Ray LA (2011) Risk-taking and alcohol use disorders symptomatology in a sample of problem drinkers. Exp Clin Psychopharmacol 19:361–370. https://doi.org/10.2217/FON.09.6.Dendritic

Ateş Çöl I, Sönmez MB, Vardar ME (2016) Evaluation of interoceptive awareness in alcohol-addicted patients. Noro Psikiyatr Ars 53:15–20. https://doi.org/10.5152/npa.2015.9898

Bailey AJ, Gerst K, Finn PR (2019) Intelligence moderates the relationship between delay discounting rate and problematic alcohol use. Psychol Addict Behav. https://doi.org/10.1037/adb0000471

Banca P, Lange I, Worbe Y et al (2016) Reflection impulsivity in binge drinking: behavioural and volumetric correlates. Addict Biol 21:504–515. https://doi.org/10.1111/adb.12227

Bari A, Robbins TW (2013) Inhibition and impulsivity: behavioral and neural basis of response control. Prog Neurobiol 108:44–79. https://doi.org/10.1016/j.pneurobio.2013.06.005

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7–15. https://doi.org/10.1016/0010-0277(94)90018-3

Bernhardt N, Nebe S, Pooseh S et al (2017) Impulsive decision making in young adult social drinkers and detoxified alcohol-dependent patients: a cross-sectional and longitudinal study. Alcohol Clin Exp Res 41:1794–1807. https://doi.org/10.1111/acer.13481

Betka S, Pfeifer G, Garfinkel SN et al (2017) How do self-assessment of alexithymia and sensitivity to bodily sensations relate to alcohol consumption? Alcohol Clin Exp Res 42:81–88. https://doi.org/10.1111/acer.13542

Bjork JM, Hommer DW, Grant SJ, Danube C (2004) Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1-/type 2-like traits. Alcohol 34:133–150. https://doi.org/10.1016/j.alcohol.2004.06.012

Bø R, Aker M, Billieux J, Landrø NI (2016a) Binge drinkers are fast, able to stop - but they fail to adjust. J Int Neuropsychol Soc 22:38–46. https://doi.org/10.1017/S1355617715001204

Bø R, Billieux J, Landrø NI (2016b) Which facets of impulsivity predict binge drinking? Addict Behav Rep 3:43–47. https://doi.org/10.1016/j.abrep.2016.03.001

Bø R, Billieux J, Gjerde LC et al (2017) Do executive functions predict binge-drinking patterns? Evidence from a longitudinal study in young adulthood. Front Psychol 8:1–10. https://doi.org/10.3389/fpsyg.2017.00489

Brewer R, Cook R, Bird G (2016) Alexithymia: a general deficit of interoception. R Soc Open Sci 3:150664. https://doi.org/10.1098/rsos.150664

Broos N, Schmaal L, Wiskerke J et al (2012) The relationship between impulsive choice and impulsive action: a cross-species translational study. PLoS One 7:1–9. https://doi.org/10.1371/journal.pone.0036781

Cairns E, Cammock T (1978) Development of a more reliable version of the matching familiar figures test. Dev Psychol 14:555–560. https://doi.org/10.1037//0012-1649.14.5.555

Caswell AJ, Bond R, Duka T, Morgan MJ (2015a) Further evidence of the heterogeneous nature of impulsivity. Personal Individ Differ 76:68–74. https://doi.org/10.1016/j.paid.2014.11.059

Caswell AJ, Celio MA, Morgan MJ, Duka T (2015b) Impulsivity as a multifaceted construct related to excessive drinking among UK students. Alcohol Alcohol 51:77–83. https://doi.org/10.1093/alcalc/agv070

Clark L, Robbins TW, Ersche KD, Sahakian BJ (2006) Reflection impulsivity in current and former substance users. Biol Psychiatry 60:515–522. https://doi.org/10.1016/j.biopsych.2005.11.007

Claus ED, Kiehl KA, Hutchison KE (2011) Neural and behavioral mechanisms of impulsive choice in alcohol use disorder. Alcohol Clin Exp Res 35:1209–1219. https://doi.org/10.1111/j.1530-0277.2011.01455.x

Cloninger CR, Svrakic DM, Przybeck TR (1993) A psychobiological model of temperament and character. Arch Gen Psychiatry 50:975–990. https://doi.org/10.1001/archpsyc.1993.01820240059008

Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD (1994) The temperament and character inventory (TCI): a guide to its development and use. Center for Psychology of Personality Washington University, St. Louis

Cloninger RC, Sigvardsson S, Bohman M (1996) Type I and type II alcoholism in a treatment sample. Alcohol Health Res World 20:18–23. https://doi.org/10.1016/0091-3057(94)90388-3

Cohen-Gilbert JE, Nickerson LD, Sneider JT et al (2017) College binge drinking associated with decreased frontal activation to negative emotional distractors during inhibitory control. Front Psychol 8:1–12. https://doi.org/10.3389/fpsyg.2017.01650

Conger JJ (1956) Alcoholism: theory, problem and challenge. II. Reinforcement theory and the dynamics of alcoholism. Q J Stud Alcohol 17:296–305

Cooper ML, Frone MR, Russell M, Mudar P (1995) Drinking to regulate positive and negative emotions: a motivational model of alcohol use. J Pers Soc Psychol 69:990–1005. https://doi.org/10.1037/0022-3514.69.5.990

Coskunpinar A, Dir AL, Cyders MA (2013) Multidimensionality in impulsivity and alcohol use: a meta-analysis using the UPPS model of impulsivity. Alcohol Clin Exp Res 37:1441–1450. https://doi.org/10.1111/acer.12131

Courtney KE, Arellano R, Barkley-Levenson E et al (2012) The relationship between measures of impulsivity and alcohol misuse: an integrative structural equation modeling approach. Alcohol Clin Exp Res 36:923–931. https://doi.org/10.1111/j.1530-0277.2011.01635.x

Curcio AL, George AM (2011) Selected impulsivity facets with alcohol use/problems: the mediating role of drinking motives. Addict Behav 36:959–964. https://doi.org/10.1016/j.addbeh.2011.05.007

Cyders MA, Smith GT (2007) Mood-based rash action and its components: positive and negative urgency. Personal Individ Differ 43:839–850. https://doi.org/10.1016/j.paid.2007.02.008

Cyders MA, Smith GT (2008) Emotion-based dispositions to rash action: positive and negative urgency. Psychol Bull 134:807–828. https://doi.org/10.1037/a0013341

Cyders MA, Flory K, Rainer S, Smith GT (2009) The role of personality dispositions to risky behavior in predicting first-year college drinking. Addiction 104:193–202. https://doi.org/10.1111/j.1360-0443.2008.02434.x

Cyders MA, Zapolski TCB, Combs JL et al (2010) Experimental effect of positive urgency on negative outcomes from risk taking and on increased alcohol consumption. Psychol Addict Behav 24:367–375. https://doi.org/10.1037/a0019494

Dalley JW, Robbins TW (2017) Fractionating impulsivity: neuropsychiatric implications. Nat Rev Neurosci 18:158–171. https://doi.org/10.1038/nrn.2017.8

Dalley JW, Everitt BJ, Robbins TW (2011) Impulsivity, compulsivity, and top-down cognitive control. Neuron 69:680–694. https://doi.org/10.1016/j.neuron.2011.01.020

de Haan L, Egberts ACG, Heerdink ER (2015) The relation between risk-taking behavior and alcohol use in young adults is different for men and women. Drug Alcohol Depend 155:222–227. https://doi.org/10.1016/j.drugalcdep.2015.07.013

de Wit H (2009) Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addict Biol 14:22–31. https://doi.org/10.1111/j.1369-1600.2008.00129.x

Del Boca FK, Darkes J, Greenbaum PE, Goldman MS (2004) Up close and personal: temporal variability in the drinking of individual college students during their first year. J Consult Clin Psychol 72:155–164. https://doi.org/10.1037/0022-006X.72.2.155

Dick DM, Smith G, Olausson P et al (2010) Understanding the construct of impulsivity and its relationship to alcohol use disorders. Addict Biol 15:217–226. https://doi.org/10.1111/j.1369-1600.2009.00190.x.Understanding

Dinc L, Cooper AJ (2015) Positive affective states and alcohol consumption: the moderating role of trait positive urgency. Addict Behav 47:17–21. https://doi.org/10.1016/j.addbeh.2015.03.014

Dom G, D'haene P, Hulstijn W, Sabbe B (2006) Impulsivity in abstinent early- and late-onset alcoholics: differences in self-report measures and a discounting task. Addiction 101:50–59. https://doi.org/10.1111/j.1360-0443.2005.01270.x

Dougherty DM, Marsh DM, Mathias CW (2002) Immediate and delayed memory tasks: a computerized behavioral measure of memory, attention, and impulsivity. Behav Res Meth Instrum Comput 34:391–398. https://doi.org/10.3758/BF03195467

Dougherty DM, Mathias CW, Marsh DM, Jagar AA (2005) Laboratory behavioral measures of impulsivity. Behav Res Methods 37:82–90. https://doi.org/10.3758/BF03206401

Dvorak RD, Pearson MR, Sargent EM et al (2016) Daily associations between emotional functioning and alcohol involvement: moderating effects of response inhibition and gender. Drug Alcohol Depend 163:S46–S53. https://doi.org/10.1016/j.drugalcdep.2015.09.034

Evenden JL (1999a) Varieties of impulsivity. Psychopharmacology 146:348–361. https://doi.org/10.1007/PL00005481

Evenden JL (1999b) Impulsivity: a discussion of clinical and experimental findings. J Psychopharmacol 13:180–192. https://doi.org/10.1177/026988119901300211

Fernández-Artamendi S, Martínez-Loredo V, Grande-Gosende A et al (2018) What predicts what? Self-reported and behavioral impulsivity and high-risk patterns of alcohol use in Spanish early adolescents: a 2-year longitudinal study. Alcohol Clin Exp Res 42:2022–2032. https://doi.org/10.1111/acer.13852

Fernie G, Cole JC, Goudie AJ, Field M (2010) Risk-taking but not response inhibition or delay discounting predict alcohol consumption in social drinkers. Drug Alcohol Depend 112:54–61. https://doi.org/10.1016/j.drugalcdep.2010.05.011

Fineberg NA, Potenza MN, Chamberlain SR et al (2010) Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. Neuropharmacology 35:591–604. https://doi.org/10.1038/npp.2009.185

Fineberg NA, Chamberlain SR, Goudriaan AE et al (2014) New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. CNS Spectr 19:69–89. https://doi.org/10.1017/S1092852913000801

Fox HC, Bergquist KL, Gu P, Sinha R (2010) Interactive effects of cumulative stress and impulsivity on alcohol consumption. Alcohol Clin Exp Res 34:1376–1385. https://doi.org/10.1111/j.1530-0277.2010.01221.x

Gerst KR, Gunn RL, Finn PR (2017) Delay discounting of losses in alcohol use disorders and antisocial psychopathology: effects of a working memory load. Alcohol Clin Exp Res 41:1768–1774. https://doi.org/10.1111/acer.13472

Gierski F, Benzerouk F, De Wever E et al (2017) Cloninger's temperament and character dimensions of personality and binge drinking among college students. Alcohol Clin Exp Res 41:1970–1979. https://doi.org/10.1111/acer.13497

Goudriaan AE, Oosterlaan J, De Beurs E, Van Den Brink W (2006) Neurocognitive functions in pathological gambling: a comparison with alcohol dependence, Tourette syndrome and normal controls. Addiction 101:534–547. https://doi.org/10.1111/j.1360-0443.2006.01380.x

Gowin J, Sloan ME, Swan JE et al (2019) The relationship between delay discounting and alcohol dependence in individuals with and without comorbid psychopathology. Psychopharmacology 236:775–785. https://doi.org/10.1007/s00213-018-5113-3

Haase L, Stewart JL, Youssef B et al (2016) When the brain does not adequately feel the body: links between low resilience and interoception. Biol Psychol 113:37–45. https://doi.org/10.1016/j.biopsycho.2015.11.004

Hamilton KR, Sinha R, Potenza MN (2012) Hazardous drinking and dimensions of impulsivity, behavioral approach, and inhibition in adult men and women. Alcohol Clin Exp Res 36:434–449. https://doi.org/10.1111/j.1530-0277.2011.01708.x

Hatchard T, Mioduszewski O, Fall C et al (2017) Neural impact of low-level alcohol use on response inhibition: an fMRI investigation in young adults. Behav Brain Res 329:12–19. https://doi.org/10.1016/j.bbr.2017.04.032

Henges AL, Marczinski CA (2012) Impulsivity and alcohol consumption in young social drinkers. Addict Behav 37:217–220. https://doi.org/10.1016/J.ADDBEH.2011.09.013

Herman AM, Duka T (2018) Facets of impulsivity and alcohol use: what role do emotions play? Neurosci Biobehav Rev:1–15. https://doi.org/10.1016/j.neubiorev.2018.08.011

Herman AM, Critchley HD, Duka T (2018a) The role of emotions and physiological arousal in modulating impulsive behaviour. Biol Psychol 133:30–43. https://doi.org/10.1016/j.biopsycho.2018.01.014

Herman AM, Critchley HD, Duka T (2018b) Risk-taking and impulsivity: the role of mood states and interoception. Front Psychol 9:1–11. https://doi.org/10.3389/fpsyg.2018.01625

Herman AM, Critchley HD, Duka T (2019a) Binge drinking is associated with attenuated frontal and parietal activation during successful response inhibition in fearful context. Eur J Neurosci 50(3):2297–2310. https://doi.org/10.1111/ejn.14108

Herman AM, Rae CL, Critchley HD, Duka T (2019b) Interoceptive accuracy predicts nonplanning trait impulsivity. Psychophysiology 56:e13339. https://doi.org/10.1111/psyp.13339

Hogg BYJ, Evans PLC, Adrian H (1975) Stimulus generalization following extra-dimensional training in educationally subnormal (severely) children. Br J Psychol 66:211–224

Jakubczyk A, Klimkiewicz A, Mika K et al (2013) Psychosocial predictors of impulsivity in alcohol-dependent patients. J Nerv Ment Dis 201:43–47. https://doi.org/10.1097/NMD.0b013e31827aaf9d

Jakubczyk A, Skrzeszewski J, Trucco EM et al (2019) Interoceptive accuracy and interoceptive sensibility in individuals with alcohol use disorder–different phenomena with different clinical correlations? Drug Alcohol Depend 198:34–38. https://doi.org/10.1016/j.drugalcdep.2019.01.036

Jones KA, Chryssanthakis A, Groom MJ (2014) Impulsivity and drinking motives predict problem behaviours relating to alcohol use in University students. Addict Behav 39:289–296. https://doi.org/10.1016/j.addbeh.2013.10.024

Kagan J (1965) Individual differences in the resolution of response uncertainty. J Pers Soc Psychol 2:154–160. https://doi.org/10.1037/h0022199

Kagan J, Rosman BL, Day D et al (1964) Information processing in the child: significance of analytic and reflective attitudes. Psychol Monogr Gen Appl 78:1–37

Kalinowski A, Humphreys K (2016) Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. Addiction 111:1293–1298. https://doi.org/10.1111/add.13341

Kärkkäinen O, Kupila J, Häkkinen M et al (2013) AMPA receptors in post-mortem brains of Cloninger type 1 and 2 alcoholics: a whole-hemisphere autoradiography study. Psychiatry Res Neuroimag 214:429–434. https://doi.org/10.1016/j.pscychresns.2013.09.012

Kauhanen J, Julkunen J, Salonen JT (1992) Coping with inner feelings and stress: heavy alcohol use in the context of alexithymia. Behav Med 18:121–126. https://doi.org/10.1080/08964289.1992.9936962

Kirby KN, Petry NM, Bickel WK (1999) Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. J Exp Psychol Gen 128:78–87. https://doi.org/10.1037/0096-3445.128.1.78

Kovács I, Richman MJ, Janka Z et al (2017) Decision making measured by the Iowa gambling task in alcohol use disorder and gambling disorder: a systematic review and meta-analysis. Drug Alcohol Depend 181:152–161. https://doi.org/10.1016/j.drugalcdep.2017.09.023

Lannoy S, Billieux J, Poncin M, Maurage P (2017a) Binging at the campus: motivations and impulsivity influence binge drinking profiles in university students. Psychiatry Res 250:146–154. https://doi.org/10.1016/j.psychres.2017.01.068

Lannoy S, Heeren A, Moyaerts N et al (2017b) Differential impairments across attentional networks in binge drinking. Psychopharmacology 234:1059–1068. https://doi.org/10.1007/s00213-017-4538-4

Laukkanen V, Kärkkäinen O, Kautiainen H et al (2015a) Decreased [^{3}H]naloxone binding in the dentate Gyrus of Cloninger type 1 anxiety-prone alcoholics: a postmortem whole-hemisphere autoradiography study. Alcohol Clin Exp Res 39:1352–1359. https://doi.org/10.1111/acer.12791

Laukkanen V, Kärkkäinen O, Kupila J et al (2015b) Increased metabotropic glutamate 2/3 receptor binding in the perigenual anterior cingulate cortex of Cloninger type 2 alcoholics: a whole-hemisphere autoradiography study. Alcohol Alcohol 50:62–67. https://doi.org/10.1093/alcalc/agu081

Lawrence AJ, Luty J, Bogdan NA et al (2009a) Problem gamblers share deficits in impulsive decision-making with alcohol-dependent individuals. Addiction 104:1006–1015. https://doi.org/10.1111/j.1360-0443.2009.02533.x

Lawrence AJ, Luty J, Bogdan NA et al (2009b) Impulsivity and response inhibition in alcohol dependence and problem gambling. Psychopharmacology 207:163–172. https://doi.org/10.1007/s00213-009-1645-x

Leganes-Fonteneau M, Cheang Y, Lam Y et al (2019) Interoceptive awareness is associated with acute alcohol-induced changes in subjective effects. Pharmacol Biochem Behav 181:69–76. https://doi.org/10.1016/j.pbb.2019.03.007

Lejuez CW, Read JP, Kahler CW et al (2002) Evaluation of a behavioral measure of risk taking: the balloon analogue risk task (BART). J Exp Psychol Appl 8:75–84. https://doi.org/10.1037//1076-898X.8.2.75

Lejuez CW, Magidson JF, Mitchell SH et al (2010) Behavioral and biological indicators of impulsivity in the development of alcohol use, problems, and disorders. Alcohol Clin Exp Res 34:1334–1345. https://doi.org/10.1111/j.1530-0277.2010.01217.x

Lim AC, Cservenka A, Ray LA (2017) Effects of alcohol dependence severity on neural correlates of delay discounting. Alcohol Alcohol 52:506–515. https://doi.org/10.1093/alcalc/agx015

Logan GD (1994) On the ability to inhibit thought and action: a users' guide to the stop signal paradigm. In: Dagenbach D, Carr TH (eds) Inhibitory processes in attention, memory, and language. Academic Press, San Diego, pp 189–239

López-Caneda E, Cadaveira F, Crego A et al (2012) Hyperactivation of right inferior frontal cortex in young binge drinkers during response inhibition: a follow-up study. Addiction 107:1796–1808. https://doi.org/10.1111/j.1360-0443.2012.03908.x

MacKillop J, Amlung MT, Few LR et al (2011) Delayed reward discounting and addictive behavior: a meta-analysis. Psychopharmacology 216:305–321

MacKillop J, Weafer J, Gray JC et al (2016) The latent structure of impulsivity: impulsive choice, impulsive action, and impulsive personality traits. Psychopharmacology 233:3361–3370. https://doi.org/10.1007/s00213-016-4372-0

Madden GJ, Petry NM, Johnson PS (2009) Pathological gamblers discount probabilistic rewards less steeply than matched controls. Exp Clin Psychopharmacol 17:283–290. https://doi.org/10.1037/a0016806.Pathological

Magid V, MacLean MG, Coldera CR (2007) Differentiating between sensation seeking and impulsivity through their mediated relations with alcohol use and problems. Addict Behav 32:2046–2061. https://doi.org/10.1016/j.immuni.2010.12.017.Two-stage

McCarty KN, Morris DH, Hatz LE, McCarthy DM (2017) Differential associations of UPPS-P impulsivity traits with alcohol problems. J Stud Alcohol Drugs 78:617–622. https://doi.org/10.15288/jsad.2017.78.617

Mitchell JM, Fields HL, D'Esposito M, Boettiger CA (2005) Impulsive responding in alcoholics. Alcohol Clin Exp Res 29:2158–2169

Moeller FG, Barratt ES, Dougherty DM et al (2001) Psychiatric aspects of impulsivity. Am J Psychiatry 158:1783–1793. https://doi.org/10.1176/appi.ajp.158.11.1783

Moreno M, Estevez AF, Zaldivar F et al (2012) Impulsivity differences in recreational cannabis users and binge drinkers in a university population. Drug Alcohol Depend. https://doi.org/10.1016/j.drugalcdep.2012.02.011

Morris LS, Kundu P, Baek K et al (2016) Jumping the gun: mapping neural correlates of waiting impulsivity and relevance across alcohol misuse. Biol Psychiatry 79:499–507. https://doi.org/10.1016/j.biopsych.2015.06.009

Murphy J, Brewer R, Catmur C, Bird G (2017) Interoception and psychopathology: a developmental neuroscience perspective. Dev Cogn Neurosci 23:45–56. https://doi.org/10.1016/j.dcn.2016.12.006

Nikolaou K, Field M, Duka T (2013) Alcohol-related cues reduce cognitive control in social drinkers. Behav Pharmacol 24:29–36. https://doi.org/10.1097/FBP.0b013e32835cf458

O'Halloran L, Pennie B, Jollans L et al (2018) A combination of impulsivity subdomains predict alcohol intoxication frequency. Alcohol Clin Exp Res 42:1530–1540. https://doi.org/10.1111/acer.13779

Papachristou H, Nederkoorn C, Havermans R et al (2012) Can't stop the craving: the effect of impulsivity on cue-elicited craving for alcohol in heavy and light social drinkers. Psychopharmacology 219:511–518. https://doi.org/10.1007/s00213-011-2240-5

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51:768–774. https://doi.org/10.1002/1097-4679(199511)51:6<768

Peacock A, Cash C, Bruno R, Ferguson SG (2015) Day-by-day variation in affect, arousal and alcohol consumption in young adults. Drug Alcohol Rev 34:588–594. https://doi.org/10.1111/dar.12238

Petry NM (2001) Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. Psychopharmacology 154:243–250

Potenza MN, de Wit H (2010) Control yourself: alcohol and impulsivity. Alcohol Clin Exp Res 34. https://doi.org/10.1111/j.1530-0277.2010.01214.x

Robinson ESJ, Eagle DM, Economidou D et al (2009) Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: Specific deficits in "waiting" versus "stopping". Behav Brain Res 196:310–316. https://doi.org/10.1016/j.bbr.2008.09.021

Sanchez-Roige S, Baro V, Trick L et al (2014) Exaggerated waiting impulsivity associated with human binge drinking, and high alcohol consumption in mice. Neuropsychopharmacology 39:2919–2927

Sanchez-Roige S, Stephens DN, Duka T (2016) Heightened impulsivity: associated with family history of alcohol misuse, and a consequence of alcohol intake. Alcohol Clin Exp Res 40:2208–2217. https://doi.org/10.1111/acer.13184

Sheffer CE, Christensen DR, Landes R et al (2014) Delay discounting rates: a strong prognostic indicator of relapse to smoking. Addict Behav 39:1682–1689

Simons JS, Gaher RM, Oliver MNI et al (2005) An experience sampling study of associations between affect and alcohol use and problems among college students. J Stud Alcohol 66:459–469. https://doi.org/10.15288/jsa.2005.66.459

Simons JS, Dvorak RD, Batien BD, Wray TB (2010) Event-level associations between affect, alcohol intoxication, and acute dependence symptoms: effects of urgency, self-control, and drinking experience. Addict Behav 35:1045–1053. https://doi.org/10.1016/j.addbeh.2010.07.001

Smith KW, Gierski F, Andre J et al (2017) Altered white matter integrity in whole brain and segments of corpus callosum, in young social drinkers with binge drinking pattern. Addict Biol 22:490–501. https://doi.org/10.1111/adb.12332

Stautz K, Cooper A (2013) Impulsivity-related personality traits and adolescent alcohol use: a meta-analytic review. Clin Psychol Rev 33:574–592. https://doi.org/10.1016/j.cpr.2013.03.003

Stephan RA, Alhassoon OM, Allen KE et al (2017) Meta-analyses of clinical neuropsychological tests of executive dysfunction and impulsivity in alcohol use disorder. Am J Drug Alcohol Abuse 43:24–43. https://doi.org/10.1080/00952990.2016.1206113

Stephens DN, Duka T (2008) Cognitive and emotional consequences of binge drinking: role of amygdala and prefrontal cortex. Philos Trans R Soc B Biol Sci 363:3169–3179. https://doi.org/10.1098/rstb.2008.0097

Stevens L, Verdejo-García A, Roeyers H et al (2015) Delay discounting, treatment motivation and treatment retention among substance-dependent individuals attending an in inpatient detoxification program. J Subst Abus Treat 49:58–64. https://doi.org/10.1016/j.jsat.2014.08.007

Swendsen JD, Tennen H, Carney MA et al (2000) Mood and alcohol consumption: an experience sampling test of the self-medication hypothesis. J Abnorm Psychol 109:198–204. https://doi.org/10.1037/0021-843X.109.2.198

Taylor GJ (2000) Recent developments in alexithymia theory and research. Can J Psychiatr 45:134–142. https://doi.org/10.1177/070674370004500203

Taylor GJ, Bagby RM, Parker JDA (2003) The 20-item Toronto alexithymia scale. IV. Reliability and factorial validity in different languages and cultures. J Psychosom Res 55:277–283

Townshend JM, Duka T (2002) Patterns of alcohol drinking in a population of young social drinkers: a comparison of questionnaire and diary measures. Alcohol Alcohol 37:187–192. https://doi.org/10.1093/alcalc/37.2.187

Townshend JM, Kambouropoulos N, Griffin A et al (2014) Binge drinking, reflection impulsivity, and unplanned sexual behavior: impaired decision-making in young social drinkers. Alcohol Clin Exp Res 38:1143–1150. https://doi.org/10.1111/acer.12333

Tran J, Teese R, Gill PR (2018) UPPS-P facets of impulsivity and alcohol use patterns in college and noncollege emerging adults. Am J Drug Alcohol Abuse. https://doi.org/10.1080/00952990.2018.1503280

Um M, Whitt ZT, Revilla R et al (2019) Shared neural correlates underlying addictive disorders and negative urgency. Brain Sci 9:36. https://doi.org/10.3390/brainsci9020036

Van Den Bos W, McClure SM (2013) Towards a general model of temporal discounting. J Exp Anal Behav 99:58–73. https://doi.org/10.1002/jeab.6

Voon V, Irvine MA, Derbyshire K et al (2014) Measuring "waiting" impulsivity in substance addictions and binge eating disorder in a novel analogue of rodent serial reaction time task. Biol Psychiatry 75:148–155. https://doi.org/10.1016/j.biopsych.2013.05.013

Vuchinich RE, Simpson CA (1998) Hyperbolic temporal discounting in social drinkers and problem drinkers. Exp Clin Psychopharmacol 6:292–305. https://doi.org/10.1037/1064-1297.6.3.292

Wardell JD, Quilty LC, Hendershot CS (2016) Impulsivity, working memory, and impaired control over alcohol: a latent variable analysis. Psychol Addict Behav 30:544–554. https://doi.org/10.1037/adb0000186

Wetherill RR, Castro N, Squeglia LM, Tapert SF (2013a) Atypical neural activity during inhibitory processing in substance-Naïve youth who later experience alcohol-induced blackouts. Drug Alcohol Depend 128:243–249. https://doi.org/10.1016/j.drugalcdep.2012.09.003

Wetherill RR, Squeglia LM, Yang TT, Tapert SF (2013b) A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. Psychopharmacology 230:663–671. https://doi.org/10.1007/s00213-013-3198-2

Whelan R, Conrod PJ, Poline J-B et al (2012) Adolescent impulsivity phenotypes characterized by distinct brain networks. Nat Neurosci 15:920–925. https://doi.org/10.1038/nn.3092

Whiteside SP, Lynam DR (2001) The five factor model and impulsivity: using a structural model of personality to understand impulsivity. Personal Individ Differ 30:669–689. https://doi.org/10.1016/S0191-8869(00)00064-7

Winstanley CA, Olausson P, Taylor JR, Jentsch JD (2010) Insight into the relationship between impulsivity and substance abuse from studies using animal models. Alcohol Clin Exp Res 34:1306–1318. https://doi.org/10.1111/j.1530-0277.2010.01215.x

Worhunsky PD, Fallahi CR, Potenza MN et al (2016) A preliminary prospective study of an escalation in 'maximum daily drinks', Fronto-parietal circuitry and impulsivity-related domains in young adult drinkers. Neuropsychopharmacology 41:1637–1647. https://doi.org/10.1038/npp.2015.332

Zack M, Toneatto T, MacLeod CM (2002) Anxiety and explicit alcohol-related memory in problem drinkers. Addict Behav 27:331–343

Zuckerman M, Eysenck S, Eysenck HJ (1978) Sensation seeking in England and America: cross-cultural, age, and sex comparisons. J Consult Clin Psychol 46:139–149. https://doi.org/10.1037/0022-006X.46.1.139