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REVIEW ARTICLE

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Neurochemical substrates linked to impulsive and compulsive phenotypes in addiction: A preclinical perspective

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Abstract

Drug compulsion manifests in some but not all individuals and implicates multifaceted processes including failures in top-down cognitive control as drivers for the hazardous pursuit of drug use in some individuals. As a closely related construct, impulsivity encompasses rash or risky behaviour without foresight and underlies most forms of drug taking behaviour, including drug use during adverse emotional states (i.e., negative urgency). While impulsive behavioural dimensions emerge from drug-induced brain plasticity, burgeoning evidence suggests that impulsivity also predates the emergence of compulsive drug use. Although the neural substrates underlying the apparently causal relationship between trait impulsivity and drug compulsion are poorly understood, significant advances have come from the interrogation of defined limbic cortico-striatal circuits involved in motivated behaviour and response inhibition, together with chemical neuromodulatory influences from the ascending neurotransmitter systems. We review what is presently known about the neurochemical mediation of impulsivity, in its various forms, and ask whether commonalities exist in the neurochemistry of compulsive drug-motivated behaviours that might explain individual risk for addiction.

KEYWORDS

dopamine, GABA, glutamate, neuromodulation, noradrenaline, prefrontal cortex, serotonin, striatum

Abbreviations: 5-CSRTT, 5-choice serial reaction time task; 5-HT, serotonin; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ACC, anterior cingulate cortex; ADHD, attention-deficit hyperactivity disorder; aDLS, anterior dorsolateral striatum; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BIS-11, Barratt Impulsiveness Scale (version 11); CeA, central nucleus of the amygdala; DA, dopamine; DDT, delay-discounting task; DLS, dorsolateral striatum; DRN, dorsal raphé nucleus; DSM-5, Diagnostic and Statistical Manual of Mental Disorders (Fifth edition); GABA, gamma-aminobutyric acid; GAD, glutamate decarboxylase; IL, infralimbic cortex; LTD, long-term depression; mPFC, medial prefrontal cortex; MRS, magnetic resonance spectroscopy; NA, noradrenaline; NAcb, nucleus accumbens; NAcbC, nucleus accumbens core; NAcbS, nucleus accumbens shell; NMDA, *N*-methyl-D-aspartic acid; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; PrL, prelimbic cortex; PTZ, pentylenetetrazol; RDT, risky decision making task; SIP, schedule-induced polydipsia; SSRT, stop-signal reaction time; SSRTT, stop-signal reaction time task; SUD, severe substance use disorder; VTA, ventral tegmental area.

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1 | INTRODUCTION

Severe substance use disorder (SUD), herein referred to as addiction, is a brain disorder characterised by compulsive drug seeking and intake despite harmful consequences. Given the worldwide increase in drug consumption (UNODC, 2020) and the opioid epidemic in many countries (CDC, 2020), the establishment of new treatments has never been more urgent. Clinically, the compulsive quality of drug-seeking behaviour features prominently in the revised *Diagnostic and Statistical Manual of Mental Disorders*, specifically the repeated use of drugs even when it endangers the life of the user. This defining disregard for personal safety and wellbeing corresponds with increasingly risky behaviour that exemplifies addiction. Accommodating this contemporary view of addiction, experimental studies in animals have evolved from the study of drug reinforcement processes to procedures that operationalise addiction in terms of drug-seeking persistence in the face of punishment (Lüscher et al., 2020).

In this review, we assimilate recent studies on the neurochemical mediation of drug compulsive phenotypes in addiction-like behaviour and extend our analysis to impulsivity—a multidimensional trait reflecting a predisposition for rapid, premature actions without forethought and aversion for delayed and uncertain rewards (Dalley & Robbins, 2017; Evenden, 1999; Winstanley et al., 2006). Consistent with these defining features, impulsivity strongly associates with addiction, both as a vulnerability marker and consequence of drug use (Bickel et al., 2019; Ersche et al., 2010; Jentsch & Taylor, 1999; Verdejo-García et al., 2008; Weafer et al., 2014). Leaving aside the possibility that drug use weakens impulse control (an eventuality that is beyond the scope of this review), it is germane to ask [1] why trait impulsivity should increase the likelihood of developing compulsive drug-seeking and [2] whether overlaps in the neurochemistry of impulsivity and compulsivity underlie a latent variable that determines individual risk for addiction.

Impulsive and compulsive behaviours are indeed distinct in many ways but nonetheless implicate analogous failures in inhibitory control mechanisms within cortical-subcortical circuits (Fineberg et al., 2014). Understanding the precise relationship between impulsive and compulsive behaviours is an area of active research. Constructs relating to impulsive and compulsive behaviours have been viewed as diametrically opposed on the same spectrum (Fineberg et al., 2010), reflecting distinct forms of cognitive control impairment (Dalley et al., 2011; Zorrilla & Koob, 2019). Yet antecedent and drug-induced perturbations in impulsivity overlap and confer risk for the development of SUD (Everitt, 2014; Jentsch & Taylor, 1999). Recent research highlights the heritability of shared impulsive-compulsive behavioural phenotypes (Tiego et al., 2020) and the strong correspondence between co-existing impulsive and compulsive traits in humans (Chamberlain et al., 2018). Thus, impulsive and compulsive behaviours may depend on distinct cortico-striatal circuits yet implicate deficits in neurochemical signalling that similarly compromise top-down inhibitory control mechanisms. We explore this idea by first providing a concise overview of the neurochemistry of impulsivity, drawing on research mainly carried out in rodents, before reviewing the separate and overlapping neurochemical substrates of compulsive drug behaviours.

2 | NEUROCHEMICAL SUBSTRATES OF IMPULSIVITY

The assessment of impulsivity in rodents relies on analogous tasks developed for testing in humans and includes the 5-choice serial reaction time task (5-CSRTT), the delay discounting task (DDT), the stop signal reaction time task (SSRTT) and the Go/No-go task. The implementation, translational significance and behavioural neurochemistry of these widely used impulsivity tasks are discussed in detail elsewhere (Dalley & Robbins, 2017) and so are only briefly surveyed below.

Impulsivity is a multifaceted construct with psychologically and neuroanatomically distinct subtypes and can be broadly separated into impulsive choice (the tendency to accept immediate versus delayed reward) and impulsive action (a failure of motor inhibition) (Dalley et al., 2011). The construct of impulsivity also includes 'stopping' and 'waiting' components, each engaging different motor, cognitive and emotional processes. Stopping impulsivity, a type of motor impulsivity, taxes motor restraint and specifically the ability to cancel a response after initiation and can be measured with the SSRTT or the Go/No-go task. Stop signal reaction time (SSRT) depends on several independent cortico-striatal networks, encompassing the putamen and caudate (equivalent to the *dorsal striatum* in rodents), pre-supplementary motor area, right inferior frontal gyrus, insula, anterior cingulate cortex (ACC), substantia nigra and subthalamic nucleus (Whelan et al., 2012). Waiting impulsivity describes a variety of behaviours requiring temporal restraint, either until signalled or non-signalled waiting intervals have elapsed or when countering preferences for instant reward and can thus be a type of action or choice impulsivity. Waiting impulsivity behaviours mainly depend on the *ventral striatum*, specifically the core and shell of the nucleus accumbens (NAcbC, NAcbS) with distinct contributions from limbic structures depending on the behaviour assessed (Caprioli et al., 2014; Robinson, Dalley, et al., 2008; Robinson, Eagle, et al., 2008). For example, premature responses in the rodent 5-CSRTT depend on the infralimbic cortex, insula and ventral hippocampus (Belin-Rauscent et al., 2016; Chudasama et al., 2003), whereas high levels of temporal discounting and impulsivity on the DDT implicate the basolateral amygdala, hippocampus, medial and lateral orbitofrontal cortex (OFC) (Bett et al., 2015; Ucha et al., 2019; Winstanley, Theobald, Cardinal, et al., 2004). Action and choice impulsivity subtypes also include components of risk-based decision making (Dalley & Robbins, 2017), including rapid decisions made before sufficient evidence has accumulated (known as reflection impulsivity; Clark et al., 2006).

2.1 | 5-HT

The impulsivity networks receive extensive 'bottom up' modulation from the monoamine neurotransmitter systems. Serotonin (5-HT) was considered early on as a key modulator of many forms of impulsivity in rodents and non-human primates. The realisation that 5-HT depletion 'releases' behaviour suppressed by punishment

(Soubrié, 1986) was a breakthrough that catalysed efforts to refine the neurochemistry of impulsivity. Subsequently, reports emerged that forebrain 5-HT depletion in rats selectively increased premature responding on the 5-CSRTT (Harrison et al., 1999; Winstanley, Theobald, Dalley, et al., 2004) and impulsivity in the DDT (Mobini et al., 2000), thus affecting both action and choice impulsivity, respectively. Additionally, optogenetic stimulation of 5-HT neurons in the dorsal raphé nucleus (DRN) reduced impulsivity on a DDT—in other words, mice shifted their preference away from small, immediate rewards (Miyazaki et al., 2014). These findings are consistent with a role of 5-HT neurons in behavioural restraint for delayed rewards. The same group later proposed that serotonergic afferents in the OFC, rather than the nucleus accumbens (NAcb), mediated the effect of DRN stimulation, which transferred to the medial prefrontal cortex (mPFC) when the timing of rewards was uncertain (Miyazaki et al., 2020). Thus, 5-HT neurons appear to promote patience for delayed rewards via signalling to the mPFC and OFC. The striatal locus of this effect is unresolved but may involve the dorsal striatum and interactions with dopamine (DA) in this region. This is supported by the finding that selective DA depletion in the rat dorsal striatum increased impulsive choice for low magnitude intracranial self-stimulation (Tedford et al., 2015).

It is noteworthy that 5-HT dysfunction was one of the first neurochemical phenotypes identified in rats screened for impulsivity in the 5-CSRTT. However, against expectations, levels of 5-HT in the mPFC, assessed using in vivo microdialysis, correlated positively with impulsivity (Dalley et al., 2002), a finding consistent with increased cortical 5-HT utilization post-mortem in rats screened for impulsivity on this task (Puumala & Sirviö, 1998) but contrary to other impulsivity phenotypes linked to low 5-HT function at this time. However, a striking positive relationship between an analogous form of impulsivity in rats was related to the ratio of 5-HT_{2A} to 5-HT_{2C} receptors in the mPFC, suggesting that 5-HT receptor subtypes play distinct roles in the modulation of motor impulsivity (Anastasio et al., 2015). Supporting this idea, 5-HT_{2C} receptor knockdown increased waiting impulsivity and upregulated 5-HT_{2A} receptor expression, indicating an opponent relationship between 5-HT_{2C} and 5-HT_{2A} receptor subtypes (Anastasio et al., 2015), conceivably co-expressed within the same population of PFC neurons (Nocjar et al., 2015). Serotonergic receptor interactions extend to the dorsomedial striatum where activation and antagonism of 5-HT_{2C} and 5-HT_{2A} receptors, respectively, decreased premature and perseverative (a form of compulsivity) responses in the 5-CSRTT following local *N*-methyl-D-aspartate (NMDA) receptor antagonism in the mPFC (Agnoli & Carli, 2012). Contrary to these findings, interventions in rodents affecting 5-HT neuronal transmission such as gene knockdown, 5-HT depletion and selective 5-HT reuptake inhibition do not affect impulsivity assessed using the SSRTT (Hausknecht et al., 2006; Bari et al., 2009; Eagle et al., 2008; Eagle et al., 2009). Such dissociations point to a selective involvement of 5-HT in specific aspects of impulsivity. The implications of these findings for drug compulsion are discussed in later sections.

2.2 | Noradrenaline and dopamine

The catecholamines DA and noradrenaline (NA) lie at the centre of many impulsive behaviours. The clearest evidence comes from administering amphetamine and other stimulant drugs, generally improving stopping impulsivity in the rodent SSRTT (Eagle et al., 2007; Feola et al., 2000) and decreasing choice impulsivity in delay-discounting procedures (Floresco et al., 2008; van Gaalen et al., 2006). Stopping efficiency appears to have its origins within PFC circuitry and NA transmission (Bari et al., 2011) and via opponent interactions between D1 and D2 receptors in the dorsomedial striatum (Eagle et al., 2011). Delay-discounting impulsivity implicates reduced DA release in the mPFC, NAcbC, NAcbS (Diergaarde et al., 2008) and altered DA receptor signalling in prefrontal regions such as the mPFC, where D1/D5 receptor stimulation increased choice for delayed rewards (Loos et al., 2010). This form of impulsivity also inversely relates to D2 receptor availability in the NAcbC, assessed using positron emission tomography (PET) and autoradiography (Barlow et al., 2018). However, stimulant effects on delay discounting depend critically on the functional integrity of the 5-HT systems (Winstanley et al., 2003), a salutary lesson that interactions between the amine transmitters often underlie impulsivity phenotypes (Dalley & Roiser, 2012).

The mesolimbic DA system further modulates premature responding in the 5-CSRTT, with DA depletion in the NAcb greatly reducing this form of impulsivity (Cole & Robbins, 1989). Infusions of a D1 receptor antagonist decreased premature responses whether given in the NAcbS or NAcbC (Pattij et al., 2007) implying behavioural activation to depend on D1 receptors in these regions. Following systemic amphetamine administration or disinhibiting lesions of the PFC, NAcbC infusions of D2 antagonists attenuated premature responding (Pattij et al., 2007; Pezze et al., 2009). Opposing these effects, blocking D2-like receptors in the NAcbS increased premature responding (Besson et al., 2010), consistent with trait impulsivity correlating with low D2 receptor binding in this region (Jupp et al., 2013). These findings imply that inhibitory presynaptic D2 receptors may be selectively downregulated in the NAcbS of trait impulsive rats, in turn leading to increased synaptic DA release. Evidence that intra-NAcbS administration of the selective NA reuptake inhibitor, atomoxetine, reduces premature responding (Economidou et al., 2012) lends further support to interactive relationships between the amine neurotransmitters.

2.3 | Glutamate

As the backbone of the impulsivity networks, glutamate has been widely researched in recent years (Carli & Invernizzi, 2014; Ucha et al., 2019; Weidacker et al., 2020; Yates & Bardo, 2017), with glutamatergic and gamma-aminobutyric acid (GABA)-ergic interactions within and between the PFC/OFC and basal ganglia mediating different aspects of inhibitory control. To illustrate this point, rat PFC neurons encode waiting intervals by ramping activity upwardly

or downwardly to the expected timing of rewards (Donnelly et al., 2015) and target the dorsomedial striatum to mediate proactive inhibitory control (Terra et al., 2020), perhaps by shifting the balance between the direct (Go) and indirect (No-Go) striatal pathways (Dunovan et al., 2015). The PFC, especially the more ventral infralimbic cortex, plays an important role in the regulation of waiting impulsivity. Thus, locally administered NMDA receptor antagonists in this subregion (Benn & Robinson, 2014; Murphy et al., 2005) weakened impulse control and increased premature responding in the 5-CSRTT. Further implicating PFC glutamatergic dysfunction in impulse control, an altered subunit composition of NMDA receptors was recently identified in trait impulsive rats. Rats deemed high-impulsive on a simple serial reaction time task, showed low expression of GluN1 and GluN2A but increased expression of GluN2B and phosphorylated GluN2B compared with low-impulsive rats (Davis-Reyes et al., 2019). Such findings reinforce translational interest in the GluN2B subunit as a target to treat impulsive and compulsive disorders (Higgins et al., 2016).

In humans, glutamate levels in the ACC, assessed using magnetic resonance spectroscopy (MRS), correlated positively with impulsive symptoms in subjects with attention-deficit hyperactivity disorder (ADHD) (Bauer et al., 2018; Ende et al. 2016). Similar findings were found in relation to SUD using the Barratt Impulsiveness Scale (Li et al., 2020), which collectively highlight an involvement of glutamate signalling in prefrontal cortical regions in impulsive behaviour.

2.4 | GABA

GABA-ergic neurons in cortical microcircuits contribute to a variety of cognitive control processes, including working memory (Auger & Floresco, 2015), attention (Auger & Floresco, 2017; Paine et al., 2015) and cognitive flexibility (Page et al., 2018; Reichel et al., 2015). In rodents, an MRS-GABA study revealed decreased GABA levels in the ventral striatum of high-impulsive rats in the 5-CSRTT (Sawiak et al., 2016). Grey matter density in the core subregion of the NAcb was also decreased in these animals and was accompanied by reduced expression of glutamate decarboxylase, the rate-limiting enzyme responsible for GABA synthesis and synaptic proteins, such as spinophilin (Caprioli et al., 2014). Validating these findings, fast-spiking GABA-ergic neurons in the NAcb, was recently shown to restrain behaviour and lessen the likelihood of impulsive responses (Pisansky et al., 2019). In the lateral OFC, but not the medial OFC, lower gene expression of the α1 $GABA_A$ receptor subunit correlated with impulsive action but not impulsive choice in rats (Ucha et al., 2019). In humans, reduced MRS-GABA levels in the PFC correlated with risky and impulsive decision making (Boy et al., 2011; Weidacker et al., 2020), with Barratt Impulsiveness Scale impulsivity scores correlating negatively with MRS GABA levels in the PFC and ACC (Ende et al. 2016; Li et al., 2020). Finally, reductions in GABA levels in the inferior frontal gyrus were found to underlie SSRT impulsivity (Murley et al., 2020), suggesting that multiple subtypes of impulsivity implicate diminished GABA-ergic function in several cortico-striatal regions.

The above synopsis, summarised in Table 1, highlights distinct nodes within the stopping and waiting impulsivity networks that depend on separate and interacting contributions from the ascending monoaminergic systems and amino-acid neurotransmitters. We recognise that our analysis is far from complete and omits, for example, neuropeptides (Alcaraz-Iborra & Cubero, 2015), endocannabinoids (Ucha et al., 2019) and the cholinergic systems (Mamiya et al., 2020), but nevertheless enables the greatest volume of literature on impulsive and compulsive behaviours to be integrated. We next discuss the neurochemistry of drug compulsion as a prelude to identifying neurochemical substrates and mechanisms that overlap with impulsivity.

3 | NEUROCHEMICAL MARKERS OF DRUG COMPULSION

The transition to compulsion is hypothesised to result from impaired inhibitory response control and a progressive shift in the locus of behavioural control from ventral limbic regions of the striatum (i.e., the NAcb) to more dorsal associative and sensorimotor areas of the striatum (Everitt & Robbins, 2016; Jentsch & Taylor, 1999; Kalivas & Volkow, 2005; Lüscher et al., 2020; Porrino et al., 2004). Although experimental approaches in rodents can never fully recapitulate the complex personal and environmental reasons why humans abuse drugs, behavioural paradigms have been developed in rodents to investigate tractable components of addiction that contribute to compulsive drug seeking. Thus, contemporary procedures to assess 'addiction-like' or compulsive behaviour in rodents de-emphasise the reinforcing effects of drugs that determine individual variation in the acquisition, escalation and reinstatement of drug responses and instead probe the persistence of drug-seeking and drug-taking in the face of punishment or aversive consequences (Lüscher et al., 2020). Compulsive drug-taking is assessed by response-contingent self-administration despite concurrent punishment (e.g., a mild foot-shock or adding an unpleasant tastant like quinine to an alcohol solution) and forms one component of the three-criteria model of stimulant addiction (Deroche-Gamonet et al., 2004).

In the three-criteria model, both drug delivery and foot-shocks are delivered concurrently on an FR-5 schedule of reinforcement, with an additional foot-shock delivered during the response preceding drug delivery (i.e., FR-4). In a series of studies, the three-criteria model has been used to assess interindividual differences in clinically translatable behavioural endophenotypes in rodents and has demonstrated striking cross-species convergence. For example, high levels of trait impulsivity predict compulsive cocaine taking in rodents (Belin et al., 2008) and is also a vulnerability marker for human substance dependence (Verdejo-García et al., 2008; Verdejo-Garcia & Albein-Urios, 2021). However, in the three-criteria model, punishment is immediate and explicitly linked to the drug-taking response. In humans, this may not always be the case, where drug-taking

TABLE 1 A summary of the effects of neurochemically selective interventions on distinct forms of impulsivity in rodents

	Task	Manipulation	Mechanism of action	Route or site of administration	Effect	Reference
DA	5-CSRTT	6-hydroxydopamine	Selective neurotoxin	NAcb	↓ premature responses	Cole and Robbins (1989)
	5-CSRTT	SCH 23390	Selective D1R antagonist	NAcb	↓ premature responses	Pattij et al. (2007)
	5-CSRTT	Sulpiride administration after mPFC lesion	Selective D2/3R antagonist	NAcbC	↓ increase in premature responses caused by lesion	Pezze et al. (2009)
	5-CSRTT	Nafadotride	D3R antagonist	NAcbS NAcbC	↑ premature responses (HI) ↓ premature responses (HI)	Besson et al. (2010)
	SSRTT	Amphetamine	DA/NA reuptake inhibitor	I.P	↓ SSRT (HI)	Feola et al. (2000)
	SSRTT	Methylphenidate	DA/NA reuptake inhibitor	I.P	↓ SSRT (HI) ↑ SSRT (LI)	Eagle et al. (2007)
	SSRTT	SCH 23390 Sulpride	Selective D1R antagonist; selective D2/3R antagonist	DMS	↓ SSRT ↑ SSRT	Eagle et al. (2011)
	DDT	6-hydroxydopamine	Selective neurotoxin	DMS	↑ delay aversion	Tedford et al. (2015)
	DDT	Ibotenic acid	Neurotoxin	STN	↓ delay aversion	Winstanley et al. (2005)
	DDT	Flupenthixol	D1R/D2R antagonist	I.P	↑ delay aversion	Floresco et al. (2008)
5-HT	5-CSRTT	5,7-dihydroxytryptamine	Selective neurotoxin	ICV	↑ premature responses	Winstanley, Theobald, Dalley, et al. (2004)
	5-CSRTT	5,7-dihydroxytryptamine	Selective neurotoxin	ICV	↑ premature responses	Harrison et al. (1997)
	5-CSRTT	M100907	5-HT_{2A}R antagonist	DS	↑ premature responses	Agnoli and Carli (2012)
	5-CSRTT	Lorcaserin SB–242084	5-HT_{2C}R agonist 5-HT_{2C}R antagonist	S.C	↓ premature responses ↑ premature responses	Higgins et al. (2020)
	1-CSRTT	5-HT2CR knockdown	—	mPFC	↑ premature responses	Anastasio et al. (2015)
	DDT	5,7-dihydroxytryptamine	Selective neurotoxin	Dorsal and median raphe nuclei	↑ delay aversion	Mobini et al. (2000)
	DDT	Optogenetic stimulation	—	Dorsal raphe nucleus	↓ delay aversion	Miyazaki et al. (2014)
NA	5-CSRTT	Atomoxetine	Selective NA reuptake inhibitor	NAcbS	↓ premature responses	Economidou et al. (2012)
	5-CSRTT	Atomoxetine	Selective NA reuptake inhibitor	I.P	↓ premature responses	Robinson et al. (2008)
	5-CSRTT	Prazosin	α_1-adrenoceptor antagonist	S.C	↑ premature responses	Koskinen et al. (2003)
	DDT	Atomoxetine	Selective NA reuptake inhibitor	I.P	↓ delay aversion	Robinson et al. (2008)
	DDT	Phenylephrine	α_1-adrenoceptor agonist	I.P	↑ delay aversion	van Gaalen et al. (2006)
	SSRTT	Atomoxetine	Selective NA reuptake inhibitor	I.P	↓ SSRT	Robinson, Dalley, et al. (2008), Robinson, Eagle, et al. (2008)
	SSRTT	Atipamezole	α_2-adrenoceptor antagonist	I.P	↓ SSRT	Bari and Robbins (2013)

(Continues)

TABLE 1 (Continued)

	Task	Manipulation	Mechanism of action	Route or site of administration	Effect	Reference
	SSRTT	Atomoxetine	Selective NA reuptake inhibitor	dPL, OFC	↓ SSRT	Bari et al. (2011)
	SSRTT	Guanfacine	α_{2a}-adrenoceptor agonist	dPL	↑ SSRT	Bari et al. (2011)
GLUT	5-CSRTT	*(R)*-CPP	NMDAR antagonist	IL	↑ premature responses	Murphy et al. (2005)
	5-CSRTT	MK801	Non-competitive NMDAR antagonist	IL	↑ premature responses	Benn and Robinson (2014)
GABA	5-CSRTT	Muscimol	$GABA_AR$ agonist	IL	↑ premature responses	Murphy et al. (2012)
	SSRTT	Muscimol	$GABA_AR$ agonist	dPL, ACC	↓ SSRT	Bari et al. (2011)

Abbreviations: ↑, increased; ↓, decreased; 1-CSRTT, 1-choice serial reaction time task; 5-CSRTT, 5-choice serial reaction time task; ACC, anterior cingulate cortex; D1R, dopamine D1 receptor; D2/3R, dopamine D2/3 receptor; D2R, dopamine D2 receptor; DA, dopamine; DDT, delay-discounting task; DMS, dorsomedial striatum; dPL, dorsal prelimbic cortex; DS, dorsal striatum; GABA, γ-amino-butyric acid; $GABA_AR$, γ-amino-butyric acid B receptor$GABA_AR$, γ-amino-butyric acid A receptor; Glut, glutamate; HI, high impulsive; I.P, intraperitoneal; ICV, intracerebroventricular; IL, infralimbic cortex; LI, low impulsive; mPFC, medial prefrontal cortex; NA, noradrenaline; NAcb, nucleus accumbens; NAcbC, nucleus accumbens core; NAcbS, nucleus accumbens shell; NMDAR, *N*-methyl-D-aspartic acid receptor; OFC, orbitofrontal cortex; S.C, subcutaneous. *(R)*-CPP, 3-[(R)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid; SSRT, stop-signal reaction time; SSRTT, stop-signal reaction time task; STN, subthalamic nucleus.

responses can be associated with delayed and often probabilistic detrimental consequences. In addition, the three criteria model primarily models compulsive drug-taking and does not assess drug-seeking behaviour under the threat of punishment.

Conversely, well-established cue-controlled cocaine seeking and compulsive drug-seeking responses can be measured using second-order schedules of reinforcement paired with or without contingent foot-shocks, respectively. In such procedures, drug delivery occurs after a certain time has elapsed—the fixed interval (e.g., 15 min), with drug-seeking responses maintained by classically conditioned stimuli previously paired with a drug reinforcer. One advantage of the second-order schedule is that it can be used to probe drug-seeking behaviour in the absence of direct drug effects. Thus, an important distinction between instrumental responding during the first drug-free interval and subsequent intervals is made, the former behaviour being directly under control of the conditioned reinforcing properties of the drug-conditioned stimulus, the latter behaviour influenced also by the rate-altering effects of the drug.

So-called heterogeneous seeking-taking chain schedules index compulsive drug-seeking by requiring animals to press a 'seeking' lever, to gain access to a drug 'taking' lever, responding on which results in drug delivery. Under this schedule, compulsive drug-seeking is assessed with the introduction of an unpredictable, mild foot-shock that occurs 50% of the time after the completion of the seeking lever response (Pelloux et al., 2012). The unpredictable nature of punishment under these conditions may more closely relate to the uncertainty of adverse consequences during drug procurement in humans. Alternatively, threat of punishment and anticipation of aversive consequences has been used in conjunction with the seeking-taking chain schedule as an alternative to contingent foot-shock punishment delivered immediately after the instrumental seeking response (Vanderschuren & Everitt, 2005). After limited drug taking experience, presentation of a tone previously paired with foot-shock suppressed cocaine seeking, an effect not observed after prolonged self-administration (i.e., after an extended history of self-administration cocaine seeking was no longer suppressed by the presentation of the aversive conditioned stimulus) (Vanderschuren & Everitt, 2005).

Compulsive alcohol intake is often assessed by the addition of the bitter tastant quinine to an oral alcohol solution, rendering the solution less palatable (for review see Hopf & Lesscher, 2014). Several aspects of the human disorder are captured within the quinine model. For example, alcohol-dependent individuals will consume toxic products that contain alcohol (e.g., Eau de Cologne and antiseptics) (Leon et al., 2007), clearly demonstrating alcohol use in the face of negative consequences. This has obvious parallels with quinine adulteration and highlights the face validity of the paradigm in simulating alcohol abuse in humans. Similar to compulsive cocaine use, rats become averse-resistant to quinine after extended access to alcohol (Hopf et al., 2010), a phenotype that persists for many months (Wolffgramm & Heyne, 1991). Approximately 15% of animals with extensive alcohol self-administration exposure (~10 weeks) continue to administer alcohol when offered an alternative sugar reward. This subpopulation of rats then go on to display several addiction-like behaviours and continue to self-administer alcohol in (a) the face of foot-shock punishment and (b) after the adulteration of alcohol with quinine (Augier et al., 2018). This report, and others (Seif et al., 2013), suggests that resistance to multiple forms of punishment may be subserved by overlapping neural mechanisms and co-occur within an individual. Thus, Seif et al. showed that compulsive alcohol taking as measured by both quinine adulteration and foot-shock punishment is mediated by PFC to NAcbC circuitry (Seif et al., 2013). Indeed, preclinical circuit-mapping studies have shown impaired fronto-striatal connectivity in compulsive drug-seeking rats (Chen et al., 2013). Moreover, translationally relevant imaging

techniques have highlighted overlapping cross-species neural circuits linked to compulsive drug use (Hu et al., 2015, 2019).

Finally, for the purposes of this review, schedule-induced polydipsia (SIP) assesses the compulsive consumption of freely available water when food reward is unpredictable. Adjunctive drinking behaviour under SIP captures several hallmark features of compulsive disorders, specifically the tendency of some animals to develop drinking that is excessive, repetitive and maladaptive. Although the link between compulsive drinking and psychostimulant use has yet to be fully explored, enhanced self-administration of amphetamine is related to enhanced levels of SIP (Piazza et al., 1993) and several behavioural traits confer risk for both SIP and stimulant use. For example, rats screened for high impulsivity in the 5-CSRTT, which subsequently develop compulsive cocaine self-administration (Belin et al., 2008), develop high levels of drinking when trained on a SIP task (Belin-Rauscent et al., 2016; Higgins et al., 2020). In the sections that follow, we survey the evidence linking each of the major neurotransmitter systems with compulsive drug-seeking and drug-taking (for a summary see Table 2).

3.1 | 5-HT

The 5-HT systems have long been implicated in reward and punishment (Patkina & Lapin, 1976; Soubrie et al., 1981) with median and dorsal raphe 5-HT neurons contributing, respectively, to conditioned fear and behavioural control under punishment (Avanzi et al., 2003; Thiébot et al., 1983). Adaptations in the 5-HT systems are also widely implicated in addiction to a variety of abused drugs (for review see Müller & Homberg, 2015). In the context of compulsion, rats identified as compulsive drug seekers on a seeking-taking task showed reduced 5-HT turnover (5-HT/5-HIAA ratio) in the PFC, striatum and amygdala and decreased DA turnover in the dorsal striatum, compared with non-compulsive rats (Pelloux et al., 2012). Roughly 20% of rats developed compulsive cocaine seeking, a proportion comparable to the probability of humans giving way to stimulant addiction (Anthony et al., 1994). Importantly, the quantity of cocaine administered was no different between compulsive and non-compulsive rats, suggesting individual variability in compulsive drug-seeking was determined by other factors, most likely underlying risk variables. For example, addiction-prone, impulsive rats in the 5-CSRTT show pre-existing cortical 5-HT dysfunction, as discussed above and a reduced expression of 5-HT_{2c} receptors in the ACC and NAcbS (Besson et al., 2013). Further, in the Pelloux study above, 5-HT depletion via intracerebroventricular 5–7-DHT, or systemic administration of a 5-HT_{2C} receptor antagonist, increased levels of drug-seeking under punishment. Moreover, citalopram, a selective 5-HT reuptake inhibitor, reduced compulsive seeking in a dose-dependent manner, suggesting that reduced 5-HT forebrain signalling is causally involved in compulsive cocaine seeking.

Supporting these findings, reduced 5-HT_{2C} protein production via genetic depletion of 5-HT_{2C} receptors in the mPFC induced motor impulsivity and enhanced cocaine seeking during withdrawal (Anastasio et al., 2014). Furthermore, administration of the 5-HT_{2C} antagonist SB242084 increased compulsive drinking in the SIP procedure and increased premature responses in the 5-CSRTT, with the 5-HT_{2C} agonist CP809101 having the opposite effect, in reducing compulsive drinking and decreasing premature responding (Higgins et al., 2020). High drinking in the SIP procedure was also associated with reduced 5-HT_{2A} receptor binding in the PFC, and DOI, a 5-$HT_{2A/C}$ receptor agonist decreased water consumption when infused directly into this region (Mora et al., 2018), an effect found earlier to be mediated by 5-HT_{2A} receptors (Navarro et al., 2015). Taken together, these findings reveal a bidirectional role of 5-HT in compulsive cocaine seeking and imply specific key roles of 5-HT_{2A} and 5-HT_{2C} receptors.

3.2 | Dopamine

The ascending DA systems contribute in multifaceted ways to reward and addiction by supporting the initiation and reinforcing effects of drugs, associative learning processes and vulnerability mechanisms (Berridge & Robinson, 2016; Hyman, 2005; Koob & Volkow, 2016; Lüscher et al., 2020; Nader et al., 2002). Spiralling pathways between midbrain DA neurons and striatal subregions (Haber et al., 2000; Ikemoto, 2007) are hypothesised to underlie the shift in behavioural control over drug seeking (Everitt et al., 2008) with established seeking responses eventually transferring to the dorsal striatum and a habit-based system (Belin et al., 2013). Disconnecting intrastriatal connectivity through specific lesions of the NAcbC as well as dorsolateral striatal infusions of the DA receptor antagonist α-flupenthixol decreased cocaine seeking in rats extensively trained under a second order schedule of reinforcement (Belin & Everitt, 2008). This observed shift in behavioural control by DA reflects well-established cue-controlled cocaine-seeking, reflecting the habitual quality of drug-seeking behaviour but not necessarily compulsion per se. Nonetheless, consistent with this shift, earlier seminal studies remarkably demonstrated that neurochemical and metabolic markers in the dorsal striatum were affected by chronic, but not acute, cocaine self-administration in non-human primates (Letchworth et al., 2001; Porrino et al., 2004). Moreover, phasic DA release decreased in the ventromedial striatum (VMS) and increased in the dorsolateral striatum after several weeks of cocaine exposure (Willuhn et al., 2012), while DA release in the dorsal striatum, but not the ventral striatum, was evoked by response-contingent, drug-associated stimuli, during well-established cocaine seeking (Ito et al., 2002).

After extended training, compulsive alcohol seeking in a punished seeking-taking task was recently shown to depend on the DA-rich anterior dorsolateral striatum (Giuliano et al., 2019). Animals showing increased reliance on anterior dorsolateral striatum dopaminergic mechanisms were subsequently more likely to develop compulsive alcohol seeking. As well as the dorsal striatum, D1 receptors in the NAcbS and NAcbC play a critical role in drug-seeking after punishment. Infusions of the D1-R antagonist SCH 23390 in both the NAcbS and NAcbC decreased the renewal of alcohol seeking after

TABLE 2 A summary of the effects of neurochemically selective interventions on different forms of drug-seeking and drug-taking behaviour in rodents

	Task	Manipulation	Mechanism of action	Route or site of administration	Effect	Reference
DA	Cocaine SA—SOR	Intrastriatal disconnection α-flupenthixol	D1R/D2R antagonist	NAcbC +DLS DLS	↓ cocaine-seeking ↓ cocaine-seeking	Belin and Everitt (2008)
	Alcohol SA—STCS	α-flupenthixol	D1R/D2R antagonist	aDLS	↓ alcohol-seeking	Giuliano et al. (2019)[a]
	Alcohol SA—punishment-induced abstinence	SCH 23390	Selective D1R antagonist	S.C NAcbC NAcbS	↓ alcohol-seeking ↓ alcohol-seeking ↓ alcohol-seeking	Marchant and Kaganovsky (2015)[a]
	Cocaine SA—conflict based relapse model	Flupenthixol Amphetamine	D1R/D2R antagonist; DA/NA reuptake inhibitor	NAcbC NAcbC	↓ cue-evoked reinstatement ↑ cue-evoked reinstatement	Saunders et al. (2013)
	Cocaine SA—SOR	SB–277011-A	Selective D3R antagonist	Systemic	↓ cocaine-seeking	Di Ciano et al. (2003)
	Cocaine SA—SOR	α-flupenthixol	D1R/D2R antagonist	DS	↓ cocaine-seeking	Vanderschuren et al. (2005)
5-HT	Cocaine SA—STCS	mCPP SB–242084 Citalopram 5,7-DHT	Partial 5-HT_{2C}R agonist; selective 5-HT_{2C}R antagonist; SSRI; selective serotonin neurotoxin	I.P I.P I.P ICV	↓ cycles-completed ↑ cycles-completed ↓ cycles-completed ↑ cycles-completed	Pelloux et al. (2012)[a]
	Cocaine SA	5-HT2CR knockdown	—	mPFC	↑ cocaine cue reactivity after forced abstinence	Anastasio et al. (2014)
	SIP	Lorcaserin CP–8091010 SB–242084	5-HT_{2C}R agonist; selective 5-HT_{2C}R agonist; selective 5-HT_{2C}R antagonist	S.C S.C I.P	↓ water intake ↓ water intake ↑ water intake (LD)	Higgins et al. (2020)
	SIP	DOI	5-$HT_{2A/C}$R agonist	mPFC	↓ water intake (HD)	Mora et al. (2018)
	SIP	Citalopram DOI SB–242084	SSRI; 5-$HT_{2A/C}$R agonist; selective 5-HT_{2C}R antagonist	I.P S.C I.P	↓ water intake (HD) ↓ water intake (HD) ↑ water intake (HD)	Navarro et al. (2015)
NA	Cocaine SA—saline, cocaine or foot-shock-induced reinstatement	Clonidine Lofexidine Guanabenz	α_2-adrenoceptor agonists	I.P	↓ fs-induced reinstatement ↓ fs-induced reinstatement ↓ fs-induced reinstatement	Erb et al. (2000)
	Cocaine SA—cue- and cocaine-induced reinstatement	Clonidine UK–14,304 Guanfacine Moxonidine	I1 / α_2-adrenoceptor agonist; I1 / α_2-adrenoceptor agonist; α_2-adrenoceptor agonist; I1 / α_2-adrenoceptor agonist	I.P	↓ cue-induced reinstatement ↓ cue-induced reinstatement ↓ cue-induced reinstatement ↓ cue-induced reinstatement	Smith and Aston-Jones (2011)

(Continues)

TABLE 2 (Continued)

	Task	Manipulation	Mechanism of action	Route or site of administration	Effect	Reference
	Cocaine SA—cue-induced reinstatement after forced abstinence	Prazosin Terazosin Phenylephrine RX 281001	Selective α_1-adrenoceptor antagonist; selective α_1-adrenoceptor antagonist; selective α_1-adrenoceptor agonist; selective α_2-adrenoceptor antagonist	VTA	↓ cue-induced reinstatement ↓ cue-induced reinstatement ↑ cue-induced reinstatement ↑ cue-induced reinstatement	Solecki et al. (2018)
	CPP, extinction, drug-induced and stress-induced reinstatement	Yohimbine BRL 44408	α_2-adrenoceptor antagonists	I.P	↑ time in cocaine compartment ↑ time in cocaine compartment	Mantsch et al. (2010)
	Cocaine SA—ShA and LgA	Prazosin	α_1-adrenoceptor antagonist	I.P	↓ breakpoint (LgA)	Wee et al. (2008)
	Heroin SA—ShA and LgA	Prazosin	α_1-adrenoceptor antagonist	I.P	↓ heroin intake (LgA)	Greenwell et al. (2009)
	Cocaine SA—STCS	Atomoxetine	Selective NA reuptake inhibitor	I.P	↓ relapse to cocaine seeking after punishment induced abstinence	Economidou et al. (2009)[a]
	SIP	Atomoxetine	Selective NA reuptake inhibitor	I.P	↓ water intake	Ansquer et al. (2014)
GLUT	Cocaine SA—extinction-reinstatement	AMPA Cis-ACDA	AMPAR agonist; NMDAR agonist	NAcb	↑ reinstatement ↑ reinstatement	Cornish et al. (1999)
	Heroin SA—extinction-reinstatement	CNQX	AMPA/Kainate receptor antagonist	NAcbC	↓ reinstatement	LaLumiere and Kalivas (2008)
	Cocaine SA—SOR	LY293558	AMPA/Kainate receptor antagonist	NAcbC	↓ cocaine-seeking	Di Ciano and Everitt (2001)
	Cocaine SA—SOR	LY293558	AMPA/Kainate receptor antagonist	DS	↓ cocaine-seeking	Vanderschuren et al. (2005)
	Cocaine SA—SOR	*N*-acetylcysteine	Synaptic glutamate release inhibitor	I.P	↓ cocaine-seeking	Murray et al. (2012)
	SIP	Memantine Lamotrigine	NMDAR antagonist; sodium channel blocker	I.P	↓ water intake (HD) ↓ water intake (HD)	Prados-Pardo et al. (2019)
GABA	Alcohol SA—multiple models	GAT−3 transporter knockdown	—	Amygdala	↑ alcohol choice	Augier et al. (2018)[a]
	Cocaine SA—STCS	Muscimol Baclofen	$GABA_AR$ agonist; $GABA_BR$ agonist	CeA	↑ cocaine SA ↑ cocaine SA	Sun and Yuill (2020)[a]
	Cocaine/Heroin SA—SOR	Baclofen	$GABA_BR$ agonist	I.P	↓ cocaine-seeking ↓ heroin-seeking	Di Ciano and Everitt (2003)
	Alcohol SA—extinction-reinstatement	Baclofen	$GABA_BR$ agonist	I.P	↓ reinstatement	Maccioni et al. (2008)

(Continues)

TABLE 2 (Continued)

Task	Manipulation	Mechanism of action	Route or site of administration	Effect	Reference
Chronic alcohol choice—extinction-reinstatement and Cocaine SA—extinction-reinstatement	Baclofen CMPPE	$GABA_BR$ agonist; $GABA_BR$ positive allosteric modulator	I.P	↓ reinstatement (alcohol) ↓ reinstatement (cocaine) ↓ reinstatement (alcohol) ↓ reinstatement (cocaine)	Vengeliene et al. (2018)
SIP	PTZ	$GABA_AR$ antagonist	Systemic	↓ water intake	López-Grancha et al. (2008)

Abbreviations: (*R*)-CPP, 3-[(R)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid; ↑, increased; ↓, decreased; 5,7-DHT, 5,7-dihydroxytryptamine; aDLS, anterior dorsolateral striatum; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CeA, central amygdala; *cis*-ACDA, 1-aminocyclobutane-*cis*-1,3-dicarboxylic acid; CMPP, 2-[1-[2-(4-Chlorophenyl)-5-methylpyrazol[1,5-a]pyrimidin-7-yl]-2-piperidinyl]ethanol; CNQX, cyanquixaline (6-cyano-7-nitroquinoxaline-2,3-dione); CPP, conditioned place preference; D3R, dopamine D3 receptor; DA, dopamine; DLS, dorsolateral striatum; DOI, 2,5-dimethoxy-4-iodoamphetamine; DS, dorsal striatum; fs, foot-shock; GABA, g-amino-butyric acid; $GABA_AR$, g-amino-butyric acid B receptor; $GABA_AR$, γ-amino-butyric acid A receptor; GAT-3, GABA transporter; Glut, glutamate; HD, high drinker; I.M, intramuscular; I.P, intraperitoneal; ICV, intracerebroventricular; LD, low drinker; LgA, long-access; mPFC, medial prefrontal cortex; NA, noradrenaline; NAcb, nucleus accumbens; NAcbC, nucleus accumbens core; NAcbS, nucleus accumbens shell; NMDAR, *N*-methyl-D-aspartic acid receptor; PTZ, pentylenetetrazol; S.C, subcutaneous; SA, self-administration; ShA, short-access; SIP, schedule induced polydipsia; SOR, second order schedule of reinforcement; SSRI, selective serotonin reuptake inhibitor; STCS, seeking-taking chain schedule; VTA, ventral tegmental area.

[a]References represent studies where compulsivity has been assessed with drug-seeking or drug-taking evaluated in the face of punishment or threat of punishment.

punishment-induced abstinence (Marchant & Kaganovsky, 2015), whereas infusions of the D1/D2 receptor antagonist, α-flupenthixol, in the NAcbC decreased cue-evoked cocaine seeking in a punishment reinstatement task (Saunders et al., 2013). These studies highlight the important contribution of ventral and dorsal striatal DA in invigorating drug-seeking irrespective of the punishment schedule used to suppress responding.

More generally, DA mechanisms are implicated in a variety of compulsive behavioural phenotypes from rigid, stereotyped movements of dorsal striatal origin (Amalric & Koob, 1993), compulsive checking responses that implicate D2-like receptors (Eagle et al., 2020) and perseverative errors in reversal learning procedures (Izquierdo, 2017). In one noteworthy study, D2 receptor availability in the dorsal striatum of non-human primates, assessed using PET, was inversely related to reversal learning efficiency (Groman et al., 2011). In the same study, D2 receptor availability correlated with behavioural sensitivity to positive, but not negative, feedback during learning. Parallel findings from the same group further showed that ex vivo monoamine levels predicted reversal performance. Thus, variance in behavioural inflexibility was largely accounted for by ex vivo DA and 5-HT levels in the dorsal striatum and OFC, respectively (Groman et al., 2013).

3.3 | Noradrenaline

The locus coeruleus noradrenergic system has been widely researched in addiction-relevant behavioural processes. NA neurons are a central component of the brain stress systems that underpin increased propensity for drug-seeking during negative emotional states (Koob, 2009) and relapse to a variety of stimuli (Erb et al., 2000; España et al., 2016; Smith & Aston-Jones, 2011; Solecki et al., 2018; Weinshenker & Schroeder, 2007). To briefly illustrate this latter influence, the α2-antagonist yohimbine, which increases NA release by blocking inhibitory α2 autoreceptors, increased cue-induced seeking for cocaine in monkeys trained under a second order schedule of reinforcement, an effect that was attenuated by the α2-agonist clonidine (Lee et al., 2004). Similarly, using a conditioned place preference procedure in mice, reinstatement of a cocaine place preference was induced by forced swim stress and yohimbine and decreased by propranolol and low-dose clonidine, but not prazosin, suggesting an involvement of α1 and β2 receptors in reinstatement (Mantsch et al., 2010). These reports highlight the important role of the central noradrenergic systems in mediating drug-seeking in response to stress. In other settings, the α1 antagonist prazosin, previously shown to reduce cue-induced craving, reduced both the breakpoint for cocaine (Wee et al., 2008), a measure of motivation to acquire the drug, and heroin self-administration (Greenwell et al., 2009) in rats with a history of extended drug access.

Intrinsic impulsiveness in the 5-CSRTT has previously been shown to predict cocaine relapse and compulsive cocaine seeking. In one study (Economidou et al., 2009), outbred rats were divided into low- and high-impulsive groups and subsequently trained to

self-administer cocaine under a seeking-taking chain schedule. After stable responding was acquired, seeking was paired with a mild foot-shock for several sessions. Following punishment, drug seeking was assessed after 1 week of withdrawal. It was found that atomoxetine, a selective NA reuptake inhibitor, that also increases DA release in cortical regions, attenuated the enhanced propensity to relapse after abstinence, an effect that was more pronounced in high-impulsive rats than low-impulsive rats (Economidou et al., 2009). In a second study, extreme impulsivity phenotypes in the 5-CSRTT were related to the propensity to develop SIP (Ansquer et al., 2014). Here, chronic administration of atomoxetine reduced premature responding in high impulsive rats, as well as compulsive adjunctive drinking (Ansquer et al., 2014), although it should be noted that null effects of atomoxetine on SIP have also been reported (Higgins et al., 2020; Navarro et al., 2015). More recent studies confirm the anti-compulsivity actions of atomoxetine, for example, in compulsive marble burying (Grassi et al., 2016), a behaviour that depends on the functional integrity of the brain NA systems (Lustberg et al., 2020).

3.4 | Glutamate

The transition to addiction is hypothesised to involve a dysregulation of glutamate homeostasis and long-term changes in synaptic plasticity (van Huijstee & Mansvelder, 2015; Kalivas, 2009). Using the three-criteria model of addiction, Kasanetz et al., (2010) evaluated long-term depression (LTD) in the NAcbC following short and long access exposure to cocaine self-administration. Short access cocaine led to a suppression in NMDA receptor-dependent LTD in all subjects. However, after prolonged access to cocaine, three criteria rats (rats showing three of the addiction-like behaviours, including compulsive cocaine intake in the face of punishment) showed persistently impaired LTD whereas LTD progressively recovered in zero criteria rats (rats showing no addiction-like behaviours). Utilising the same paradigm, three criteria rats showed impaired $mGluR_{2/3}$-dependent LTD mechanisms in the dorsomedial PFC and reduced $mGluR_{2/3}$ protein expression. Moreover, the α-amino-3-hydroxy-4-isoxazolepropionic acid (AMPA) to NMDA ratio, an index of synaptic strength, increased in the prelimbic cortex (PrL) of three criteria rats (Kasanetz et al., 2013). Extending these findings, Chen et al., (2013) used a seeking-taking chain task to demonstrate that compulsive cocaine seeking manifests from PrL hypoactivity (Chen et al., 2013). Thus, optogenetic stimulation and inhibition of the PrL bi-directionally modulated compulsive cocaine seeking, both suppressing and enhancing seeking behaviour, respectively. The causally responsible output structures mediating top-down inhibitory control by the PrL remain to be fully defined but may involve in part circuits to the dorsal periaqueductal grey in the brainstem (Siciliano et al., 2019) and NAcbS (Piantadosi et al., 2020). More globally, deletion of the NMDAR subunit GluN2B in principal neurons of the cortex and hippocampus reduced punished suppression of reward seeking in mice (Radke et al., 2015). This report and others (Wang et al., 2010) highlight the important role of NMDAR subunit composition on glutamatergic signalling and reward seeking. In humans, perturbations in glutamate concentration are reported in the NAcb (Engeli et al., 2020) and caudate putamen (Ersche et al., 2020) of substance dependent individuals.

Many studies have investigated the role of specific glutamate receptor subtypes in cue-induced reinstatement of drug seeking. For example, AMPA receptor blockade in the NAcbC, but not the NAcbS, prevented reinstatement (Cornish et al., 1999). Furthermore, inactivation of the PFC → NAcbC pathway via administration of baclofen and muscimol in the PrL cortex decreased glutamate output in the NAcbC and decreased drug-seeking (LaLumiere & Kalivas, 2008). Glutamatergic mechanisms of drug-seeking have also been assessed using second order schedule of reinforcement. Thus, intra-NAcbC but not intra-NAcbS infusions of the selective AMPA/kainate receptor antagonist LY293558 dose-dependently decreased cocaine seeking in rats during the drug-free first interval and throughout the session. Infusion of the NMDA receptor antagonist AP-5 in the NAcbS produced a limited effect and no effect in the NAcbC (Di Ciano & Everitt, 2001). LY293558 (and the DA receptor antagonist α-flupenthixol) also decreased well-established cue-controlled cocaine seeking when infused in the dorsolateral striatum (Vanderschuren et al., 2005). Additionally, systemic administration of *N*-acetylcysteine, which reduces glutamate release, reduced cocaine seeking in the first drug-free interval of a second order schedule of reinforcement (Murray et al., 2012). In summary, several lines of enquiry converge on the importance of glutamatergic signalling in regulating drug-seeking behaviour. It is clear that this may be dependent on the specific location (ventral striatum versus PFC), as well as specific glutamatergic receptor subtypes.

Alcohol consumption has also been linked to glutamatergic neurotransmission. Selectively bred alcohol-preferring rats homozygous for the Grm2 stop codon, a phenotype that results in a severe loss of mGluR2 and impaired mGluR2 synaptic depression, showed increased alcohol intake (Zhou et al., 2013). In the SIP paradigm, rats showing compulsive adjunctive drinking had reduced levels of glutamate in the mPFC (Mora et al., 2018). Nevertheless, whereas *N*-acetylcysteine did not reduce water intake in high drinking animals, both the non-competitive NMDA receptor antagonist, memantine, and the glutamate/aspartate release-lowering drug, lamotrigine, did reduce SIP (Prados-Pardo et al., 2019).

In a longitudinal, pre-clinical imaging study using PET, Groman and colleagues assessed baseline levels of dopamine $D_{2/3}$ and metabotropic Glu5 (mGluR5) receptor availability in rats trained on a probabilistic reversal learning task before and after cocaine self-administration (Groman et al., 2020). Cocaine exposure significantly disrupted reversal learning performance, leading to a reduced sensitivity to, and integration of, negative feedback. These outcomes were associated with an increase in mGlu5 binding potential in the mPFC, suggesting that impaired mGlu5 signalling in this region may contribute to the formation of inflexible, perseverative-like responding (Groman et al., 2020).

3.5 | GABA

Abnormalities in GABA signalling are seen across a wide range of neuropsychiatric disorders including obsessive compulsive disorder (Li et al., 2019), schizophrenia (de Jonge et al., 2017) and addiction (Tyacke et al., 2010). In a recent study to investigate GABA-ergic mechanisms in compulsive alcohol consumption, rats were given a choice between alcohol and a high incentive sweetened solution (Augier et al., 2018). A small subset of the rats (~15%) preferred alcohol and developed addiction-like behaviours, including (a) an increased motivation to work for alcohol, as indexed by increased breakpoints in a progressive ratio task, (b) increased alcohol intake when the alcohol solution was adulterated with quinine and (c) continued alcohol intake despite foot-shock punishment. Investigation of the molecular substrates revealed a significant decrease in the GABA transporter, GAT-3, in the amygdala of alcohol-choosing rats. This was associated with increased tonic inhibition in the central nucleus of the amygdala (CeA). Moreover, short hairpin RNA knockdown of GAT-3 in the high incentive preferring group increased choice behaviour for alcohol, demonstrating a causal role of GABA-ergic mechanisms in the CeA in the development of alcohol-choice behaviour. Activation of GABA receptors in the CeA has also been shown to influence cocaine seeking under punishment (Sun & Yuill, 2020). Thus, reversibly inactivating doses of GABA agonists in the CeA increased the number of punished seeking responses. These findings are consistent with reports demonstrating increased inhibitory GABAergic transmission in rats after chronic ethanol treatment (Roberto et al., 2004). Using slice electrophysiology and in vivo microdialysis, rats treated chronically with ethanol exhibited augmented inhibitory postsynaptic potentials, an index of increased basal GABA release, relative to control animals. Moreover, both at baseline and after chronic ethanol treatment, dialysate levels of GABA were higher in rats treated chronically with ethanol than ethanol-naïve control rats (Roberto et al., 2004).

GABA signalling has also been shown to play a role in well-established cue-controlled drug seeking. Using a second order schedule of reinforcement, *Di Ciano and Everitt* showed that administration of the $GABA_B$ receptor agonist baclofen dose dependently decreased cue-controlled cocaine and heroin seeking (Di Ciano & Everitt, 2003). Moreover, baclofen and muscimol administration in the ventral tegmental area dose-dependently decreased drug-free cocaine seeking during the first interval (Di Ciano & Everitt, 2004). Systemically administered baclofen also decreased cue-induced reinstatement of alcohol-seeking in Sardinian alcohol-preferring rats (Maccioni et al., 2008), an effect also generalising to the reinstatement of heroin-seeking (Spano et al., 2007).

Several studies have also evaluated the role of GABA signalling in SIP. Administration of the $GABA_A$ receptor antagonist pentylenetetrazol decreased drinking in both high- and low-drinkers (López-Grancha et al., 2008). However, the effects of the $GABA_A$ agonist diazepam on SIP are more mixed and dependent on dose. In general, whereas low doses of diazepam increase compulsive adjunctive drinking (López-Grancha et al., 2008), higher doses reduce the temporal regulation of licking responses during intervals between food delivery (Pellon & Blackman, 1992). Although an emerging area of interest, one recent report indicates a potential role of GABA in the bed nucleus of the stria terminalis in modulating SIP (Angelis et al., 2019).

4 | SYNTHESIS AND THEORETICAL IMPLICATIONS

The now widely accepted multidimensionality of impulsivity challenges any straightforward relationship between impulsive and compulsive behavioural phenotypes in addiction. The broad construct of compulsivity also encompasses several psychological processes from rigid strategies or attentional set shifting, stereotypy, perseveration, resistance to extinction and the persistence of stimulus-response habits despite negative consequences (Robbins et al., 2012). Further challenges arise from the fact that impulsivity is often assessed in humans using subjective self-report measures, for example, the Barratt Impulsiveness Scale (Patton et al., 1995) or such factors as follows: (a) a lack of premeditation or the failure to plan carefully before acting; (b) sensation-seeking or the desire for intense, exciting experiences despite inherent risks; (c) a lack of perseverance during boring or demanding tasks; and (d) urgency or the propensity for rash or risky behaviour in positive or negative emotional settings (Whiteside & Lynam, 2001). Nevertheless, impulsivity and compulsivity both result from failures in response inhibition or top-down control and implicate aberrant reward processing and impaired insight into the consequences of inappropriately elicited actions (Dalley et al., 2011).

This review outlines the complexities of impulsive-compulsive phenotypes in addiction and highlights the shifting neural circuitries underlying the transition to compulsive drug-seeking. The main neuromodulatory systems are all implicated in different aspects of impulsive-compulsive behaviours. However, DA and 5-HT dysfunction in striatal and cortical domains is a recurring theme, especially in trait impulsive subtypes, while enhanced noradrenergic neurotransmission in the brain reduces most forms of impulsive and compulsive behaviour. Overall, our analysis reveals partially overlapping neurochemical substrates of impulsivity and compulsivity, which may underlie the recognised causal influence of trait impulsivity on the emergence of compulsive drug-seeking (Everitt, 2014). Figure 1 provides an overview of the involvement of the main neurotransmitter systems in various forms of impulsivity and compulsivity. Overall, the evidence suggests that 5-HT similarly and bidirectionally modulates impulsive and compulsive phenotypes with reduced transmission associated with both increased impulsivity and compulsivity. The exception however is SSRT impulsivity which appears to be insensitive to alterations in 5-HT function. Enhancing NA function via selective reuptake inhibition decreases the main forms of impulsivity but to date there is a paucity of data on the effects of selective NA

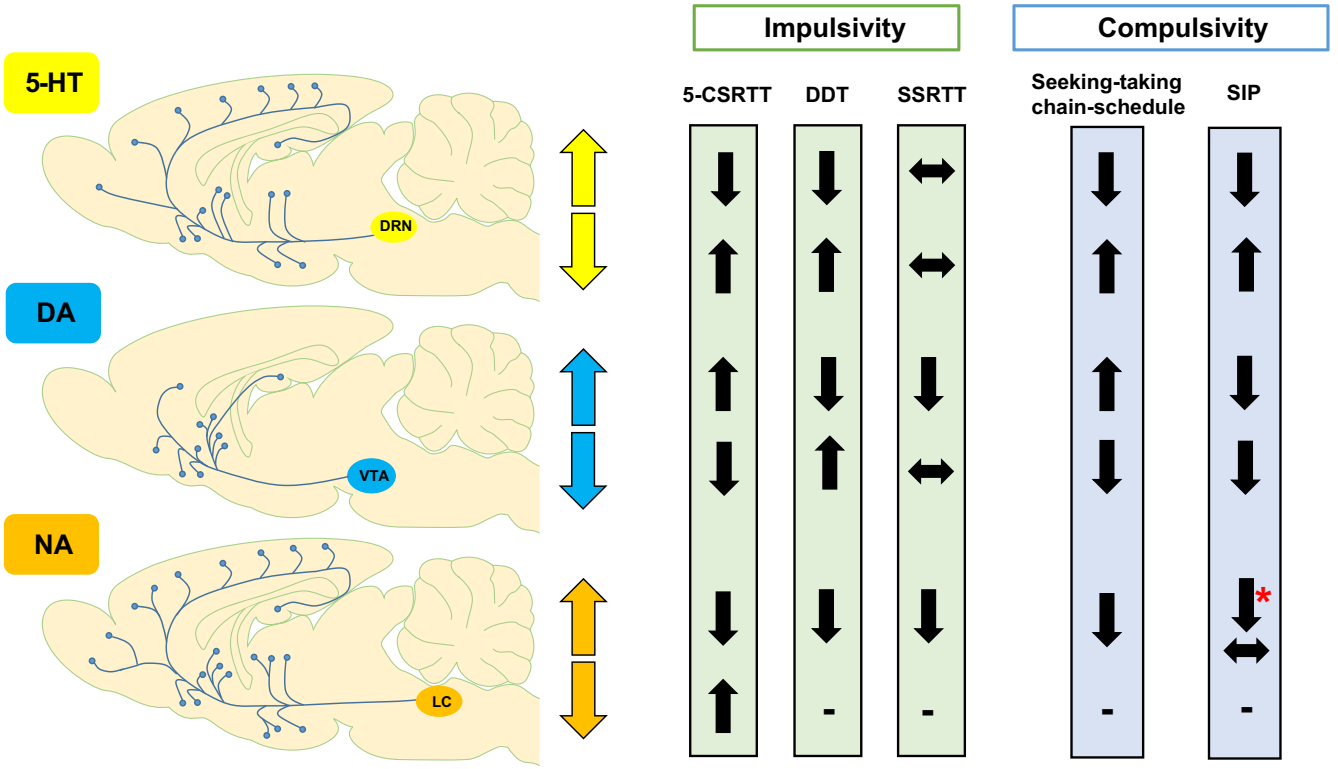

FIGURE 1 Schematic sagittal sections showing the distribution of serotonin (5-HT), dopamine (DA) and noradrenaline (NA) pathways in the rat brain (far left images). Diagrams show the locations of cell bodies in the dorsal raphé nucleus (DRN), ventral tegmental area (VTA) and locus coeruleus (LC), together with their ascending projections to the forebrain. The main effects of globally increasing or decreasing 5-HT (yellow arrows) and DA (blue arrows) on different forms of impulsivity and compulsivity are summarised in the panels on the right. These manipulations typically involve selective neurochemical depletion (e.g., effected with ICV infusions of the 5-HT neurotoxin 5,7-DHT) or systemic pharmacological agents that directly or indirectly increase synaptic neurotransmission (e.g., stimulant drugs or selective reuptake inhibitors). As few or no studies have investigated the effects of reducing NA function on impulsive-compulsive behaviours, only the effects of increased NA neurotransmission are shown (orange arrows). Upward and downward arrows denote increased and decreased impulsivity and compulsivity, respectively. Horizontal bidirectional arrows indicate no clear effect of the manipulation. The red asterisk (*) indicates that studies have reported both a decrease and null effects on SIP. A dash (-) indicates that the effects are unknown. Abbreviations: 5-CSRTT, 5-choice serial reaction time task; DDT, delay-discounting task; SIP, schedule-induced polydipsia; SSRTT, stop-signal reaction time task

depletion on impulsivity and compulsivity. Altered DA transmission generally has the opposite effects on impulsive-compulsive behaviours than 5-HT, presumably because these two monoamine systems are mutually regulated, often via antagonistic interactions (Howell & Cunningham, 2015). However, the effects of DA manipulations on impulsivity and compulsivity are more nuanced and task-dependent with the strongest alignment evident for premature responding in the 5-CSRTT and compulsive behaviour in the seeking-taking chain-schedule.

As highlighted in Figure 1, the most consistent overlap between impulsivity and compulsivity involves the 5-HT systems. Pelloux and colleagues showed that administration of the 5-HT2C receptor antagonist SB242084 increased drug seeking under punishment, while M100907, a 5-HT2A antagonist, decreased punished drug seeking (Pelloux et al., 2012). Consistent with these findings, knockdown of mPFC 5-HT2c receptor increased impulsivity in a 1-choice variant of the 5-CSRTT (Anastasio et al., 2015) while M100907 had the opposite effect (Fink et al., 2015). These findings lend support to the notion of overlapping 5-HT signalling across impulsive and compulsive phenotypes. The underlying mechanism is unclear but may relate to observations that 5-HT neurons innervating the OFC and mPFC mediate restraint for delayed and uncertain rewards (Miyazaki et al., 2020) while depletion of 5-HT from the OFC increases behavioural perseveration, a form of compulsive behaviour (Clarke et al., 2004). Evidence of diminished 5-HT levels in the PFC of stimulant-addicted individuals (Wilson et al., 1996), and following unlimited cocaine self-administration in rats (Parsons et al., 1995), links 5-HT dysfunction with impulsive-compulsive behavioural phenotypes. Also of relevance, 5-HT modulates sensitivity to negative and positive (reward) feedback (Bari et al., 2010), consistent with earlier theorising that tonic 5-HT activity signals average reward rate whereas phasic 5-HT codes prediction errors for future punishment (Daw et al., 2002). Thus, 5-HT plays a critical role in behavioural regulation and the processing of punishment signals. Through interactions with other neurotransmitters (e.g., DA), 5-HT dysfunction is a prime neurochemical substrate of impulsivity and compulsive drug-seeking.

Compulsivity can be operationally defined by the persistence of behaviour in the face of punishment. However, the relationship between impulsivity and compulsive drug-seeking/-taking requires further discussion. Punishment is a multidimensional construct that may be experienced in different ways by people addicted to substances of abuse. For example, punishment may be experienced on different temporal scales with drug use associated with potentially immediate criminal and legal consequences versus longer-term financial loss, which often manifests long after drug use. In addition, substance-dependent individuals may compulsively seek drugs after experiencing aversive stimuli within the environment related to punishment, without actually experiencing direct punishment per se. Thus, negating signals of punishment may also capture one important dimension of compulsivity. In preclinical research studies, explicit punishment is presented in several ways. For example, mild electric foot-shock may be delivered (a) alongside a drug-taking response as in the three-criteria model of addiction-like behaviour (Belin et al., 2008; Deroche-Gamonet et al., 2004); (b) alongside a probabilistic drug seeking response, as in the seeking-taking chain task (Pelloux et al., 2012) or (c) paired with a conditioned stimulus to suppress drug-seeking responses (Vanderschuren & Everitt, 2005). These procedures are based on the delivery of a foot-shock or the signalling of such with punishers delivered as a result of a particular instrumental response. Punishment is therefore immediately experienced, although it is important to note that punishment on the seeking-taking task is probabilistic in nature, and therefore, it is uncertain when the punishment will be delivered. Trait impulsivity in the 5-CSRTT predicts the persistence of cocaine-taking responses during the delivery of foot-shock (Belin et al., 2008) and also predicts higher levels of cocaine seeking after punishment induced abstinence in the seeking-taking chain task (Economidou et al., 2009). Thus, pre-existing impulsivity in the 5-CSRTT predicts compulsive responding for cocaine.

Punishment can also be modelled by the absence of an expected reward or combined with explicit punishment, for example, in such paradigms involving decision making tasks that also incorporate the risk (and delivery) of explicit punishment. For example, the risky decision-making task (RDT) combines a discounting procedure with an escalating risk of foot-shock punishment (Orsini et al., 2020; Orsini et al., 2019; Simon et al., 2009). This paradigm extends the traditional discounting paradigm (small rewards now versus larger rewards later) by the addition of a foot-shock delivered probabilistically in combination with the delivery of the large reward. Critically, the task models the discounting of delayed punishments and not delayed rewards as in the DDT. In humans, differences between discounting costs and rewards are also observed (Murphy et al., 2001), thus providing a translational impetus to dissociate the two experimentally in rodents, as in the RDT. At the behavioural level, it appears that this dissociation holds for rodents, with one report showing that discounting rewards on the DDT was unrelated to discounting risky choice on the RDT (Liley et al., 2019). One question, therefore, is how does increased levels of risky decision making, and insensitivity to delayed punishment on the RDT, relate to the self-administration of cocaine? To answer this question, Orsini and colleagues assessed performance on the RDT and then trained rats to self-administer cocaine on a short/long access paradigm (Orsini et al., 2020). Rats that showed a higher preference for the large, punished reward were more likely to escalate their cocaine intake; however, these effects were sex specific with the effect observed in females only. These results echo that observed for impulsive choice (Anker et al., 2009) and also converge with other reports demonstrating increased escalation of cocaine self-administration in rats who show deficits in the rat gambling task, an alternative measure of decision making with the risk of reward omission (Cocker et al., 2020).

Impulsive choice as measured through the delay discounting task is also linked to addiction-relevant behaviours. Thus, steeper discounting of delayed rewards, an index of increased impulsive choice, predicts increased acquisition (Perry et al., 2005) and escalation (Anker et al., 2009) of cocaine self-administration in rats. Rats with high trait levels of impulsive choice also show stronger resistance to extinction of cocaine seeking and higher rates of context-induced cocaine seeking (Broos et al., 2012). Taken together, these results suggest that both impulsive choice and impulsive action represent pre-existing vulnerability markers to the development of addiction-like behaviour. However, whereas impulsive choice may be important for the acquisition, initiation and escalation of cocaine self-administration, impulsive action is more strongly associated with compulsive cocaine-related behaviours.

Molecular imaging techniques such as PET provide the unique opportunity to bridge the translational gap between rodents and humans to probe the underlying neurochemical substrates of addiction-like behaviour. In rats and humans, diminished $D_{2/3}$ receptor availability is related to increased impulsivity across multiple dimensions (Barlow et al., 2018; Buckholtz et al., 2010; Dalley et al., 2007). Further PET-derived markers include decreased glucose metabolism in the OFC and ACC of humans with SUD, assessed using [^{18}F]-fluorodeoxyglucose (Volkow et al., 1993, 2001). Paralleling these findings, Cannella and colleagues showed that three criteria rats (rats displaying addiction-like behaviour) exhibit reduced frontal cortical glucose metabolism compared with zero criteria rats (rats displaying no addiction-like behaviour) and cocaine-naïve rats (Cannella et al., 2017). These reports and others (de Laat et al., 2018) reveal the translational utility of both longitudinal and cross-sectional PET studies to understand both vulnerability mechanisms and addiction-like behaviour, highlighting successful cross-species convergence.

As discussed throughout this review, 5-HT and DA have important and interacting roles in regulating impulsive action, impulsive choice and risky decision making (Basar et al., 2010; Winstanley et al., 2006; Yates, 2019). A potential locus for this interaction is via 5-HT neurons in the raphé nucleus which innervate the dopaminergic ventral tegmental area (Hervé et al., 1987) and substantia nigra (Clavier & Fibiger, 1977) and powerfully inhibit these regions and the terminal limbic cortico-striatal regions to which they project (Kapur & Remington, 1996). In a recent remarkable study, interactions between DA and 5-HT were investigated in seventeen non-dependent cocaine users using PET and [11C]-raclopride

to image D2 receptors in the striatum (Cox et al., 2017). Acute dietary depletion of tryptophan to reduce brain 5-HT function led to greater reductions in [11C]-raclopride binding potential in response to a low intranasal dose of cocaine (an index of DA release) than when cocaine was administered alone. Augmented reductions in [11C]-raclopride binding potential were observed in dorsal regions of the anterior and posterior putamen, and bilateral caudate, and were associated with increased drug craving. These findings show that low 5-HT increases the subjective and DA releasing effects of cocaine in non-dependent drug users. Low 5-HT states, extending into the nigrostriatal DA system, may thus be further drivers for the development of compulsive drug-seeking in susceptible individuals, a possibility meriting further research.

In conclusion, we have discussed mainstream examples of neurochemical substrates underlying impulsive and compulsive behavioural phenotypes relevant to addiction. By continuing to research the neuromodulatory systems, a clearer understanding of the neurochemical substrates of impulsive-compulsive behaviours in addiction is expected, particularly the modulation of top-down cognitive control mechanisms by the major neurotransmitter systems.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

Agnoli, L., & Carli, M. (2012). Dorsal-striatal 5-HT 2A and 5-HT 2C receptors control impulsivity and perseverative responding in the 5-choice serial reaction Time Task. *Psychopharmacology (Berl).*, *219*, 633–645. https://doi.org/10.1007/s00213-011-2581-0

Alcaraz-Iborra, M., & Cubero, I. (2015). Do Orexins contribute to impulsivity-driven binge consumption of rewarding stimulus and transition to drug/food dependence? *Pharmacology, Biochemistry and Behavior*, *134*, 31–34.

Amalric, M., & Koob, G. F. (1993). Functionally selective neurochemical afferents and efferents of the mesocorticolimbic and nigrostriatal dopamine system. *Progress in Brain Research*, *99*, 209–226.

Anastasio, N. C., Stutz, S. J., Fink, L. H. L., Swinford-Jackson, S. E., Sears, R. M., Dileone, R. J., Rice, K. C., Moeller, F. G., & Cunningham, K. A. (2015). Serotonin (5-HT) 5-HT2A receptor (5-HT2AR):5-HT2CR imbalance in medial prefrontal cortex associates with motor impulsivity. *ACS Chemical Neuroscience*, *6*, 1248–1258.

Anastasio, N. C., Stutz, S. J., Fox, R. G., Sears, R. M., Emeson, R. B., DiLeone, R. J., O'Neil, R. T., Fink, L. H., Li, D., Green, T. A., Gerard Moeller, F., & Cunningham, K. A. (2014). Functional status of the serotonin 5-HT 2C receptor (5-HT 2C R) drives interlocked phenotypes that precipitate relapse-like behaviors in cocaine dependence. *Neuropsychopharmacology*, *39*, 360–372. https://doi.org/10.1038/npp.2013.199

Angelis, S., Gregory, J. G., Hawken, E. R., & Dumont, É. C. (2019). Excessive drinking and checking in the rat model of schedule-induced polydipsia reveal impaired bi-directional plasticity at BNST GABA synapses. *bioRxiv*, 799452.

Anker, J. J., Perry, J. L., Gliddon, L. A., & Carroll, M. E. (2009). Impulsivity predicts the escalation of cocaine self-administration in rats. *Pharmacology, Biochemistry, and Behavior*, *93*(3), 343–348. https://doi.org/10.1016/j.pbb.2009.05.013

Ansquer, S., Belin-Rauscent, A., Dugast, E., Duran, T., Benatru, I., Mar, A. C., Houeto, J. L., & Belin, D. (2014). Atomoxetine decreases vulnerability to develop compulsivity in high impulsive rats. *Biological Psychiatry*, *75*, 825–832.

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the national comorbidity survey. *Experimental and Clinical Psychopharmacology*, *2*, 244–268. https://doi.org/10.1037/1064-1297.2.3.244

Auger, M. L., & Floresco, S. B. (2015). Prefrontal cortical GABA modulation of spatial reference and working memory. *International Journal of Neuropsychopharmacology*, *18*, 1–11.

Auger, M. L., & Floresco, S. B. (2017). Prefrontal cortical GABAergic and NMDA glutamatergic regulation of delayed responding. *Neuropharmacology*, *113*, 10–20.

Augier, E., Barbier, E., Dulman, R. S., Licheri, V., Augier, G., Domi, E., Barchiesi, R., Farris, S., Nätt, D., Mayfield, R. D., & Adermark, L. (2018). A molecular mechanism for choosing alcohol over an alternative reward. *Science*, *360*, 1321–1326.

Avanzi, V., Silva, R. C. B., Macedo, C. E., & Brandão, M. L. (2003). 5-HT mechanisms of median raphe nucleus in the conditioned freezing caused by light/foot-shock association. *Physiology & Behavior*, *78*, 471–477.

Bari, A., Eagle, D. M., Mar, A. C., Robinson, E. S. J., & Robbins, T. W. (2009). Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. *Psychopharmacology (Berl)*, *205*(2), 273–283.

Bari, A., Mar, A. C., Theobald, D. E., Elands, S. A., Oganya, K. C. N. A., Eagle, D. M., & Robbins, T. W. (2011). Prefrontal and monoaminergic contributions to stop-signal task performance in rats. *The Journal of Neuroscience*, *31*(25), 9254–9263. https://doi.org/10.1523/JNEUROSCI.1543-11.2011

Bari, A., & Robbins, T. W. (2013). Noradrenergic versus dopaminergic modulation of impulsivity, attention and monitoring behaviour in rats performing the stop-signal task: Possible relevance to ADHD. *Psychopharmacology*, *230*(1), 89–111. https://doi.org/10.1007/s00213-013-3141-6

Bari, A., Theobald, D. E., Caprioli, D., Mar, A. C., Aidoo-Micah, A., Dalley, J. W., & Robbins, T. W. (2010). Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learning task in rats. *Neuropsychopharmacology*, *35*, 1290–1301. https://doi.org/10.1038/npp.2009.233

Barlow, R. L., Gorges, M., Wearn, A., Niessen, H. G., Kassubek, J., Dalley, J. W., & Pekcec, A. (2018). Ventral striatal D 2/3 receptor availability is associated with impulsive choice behavior as well as limbic corticostriatal connectivity. *International Journal of Neuropsychopharmacology*, *21*, 705–715. https://doi.org/10.1093/ijnp/pyy030

Basar, K., Sesia, T., Groenewegen, H., Steinbusch, H. W. M., Visser-Vandewalle, V., & Temel, Y. (2010). Nucleus accumbens and impulsivity. *Progress in Neurobiology*, *92*(4), 533–557. https://doi.org/10.1016/j.pneurobio.2010.08.007

Bauer, J., Werner, A., Kohl, W., Kugel, H., Shushakova, A., Pedersen, A., & Ohrmann, P. (2018). Hyperactivity and impulsivity in adult attention-deficit/hyperactivity disorder is related to glutamatergic dysfunction in the anterior cingulate cortex. *World Journal of Biological Psychiatry*, *19*(7), 538–546. https://doi.org/10.1080/15622975.2016.1262060

Belin, D., Belin-Rauscent, A., Murray, J. E., & Everitt, B. J. (2013). Addiction: Failure of control over maladaptive incentive habits. *Current Opinion in Neurobiology*, *23*, 564–572.

Belin, D., & Everitt, B. J. (2008). Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron*, *57*, 432–441. https://doi.org/10.1016/j.neuron.2007.12.019

Belin, D., Mar, A. C., Dalley, J. W., Robbins, T. W., & Everitt, B. J. (2008). High impulsivity predicts the switch to compulsive cocaine-taking. *Science*, *320*, 1352–1355. https://doi.org/10.1126/science.1158136

Belin-Rauscent, A., Daniel, M. L., Puaud, M., Jupp, B., Sawiak, S., Howett, D., McKenzie, C., Caprioli, D., Besson, M., Robbins, T. W., & Everitt, B. J. (2016). From impulses to maladaptive actions: The insula is a neurobiological gate for the development of compulsive behavior. *Molecular Psychiatry*, *21*, 491–499.

Benn, A., & Robinson, E. S. J. (2014). Investigating glutamatergic mechanism in attention and impulse control using rats in a modified 5-choice serial reaction time task. *PLoS One*, *9*, e115374. https://doi.org/10.1371/journal.pone.0115374

Berridge, K. C., & Robinson, T. E. (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *American Psychologist*, *71*, 670–679.

Besson, M., Belin, D., McNamara, R., Theobald, D. E. H., Castel, A., Beckett, V. L., Crittenden, B. M., Newman, A. H., Everitt, B. J., Robbins, T. W., & Dalley, J. W. (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. https://doi.org/10.1038/npp.2009.162

Besson, M., Pelloux, Y., Dilleen, R., Theobald, D. E., Lyon, A., Belin-Rauscent, A., Robbins, T. W., Dalley, J. W., Everitt, B. J., & Belin, D. (2013). Cocaine modulation of frontostriatal expression of Zif 268, D2, and 5-HT2c receptors in high and low impulsive rats. *Neuropsychopharmacology*, *38*, 1963–1973. https://doi.org/10.1038/npp.2013.95

Bett, D., Murdoch, L. H., Wood, E. R., & Dudchenko, P. A. (2015). Hippocampus, delay discounting, and vicarious trial-and-error. *Hippocampus*, *25*(5), 643–654. https://doi.org/10.1002/hipo.22400

Bickel, W. K., Crabbe, J. C., & Sher, K. J. (2019). What is addiction? How can animal and human research be used to advance research, diagnosis, and treatment of alcohol and other substance use disorders? *Alcoholism, Clinical and Experimental Research*, *43*, 6–21. https://doi.org/10.1111/acer.13912

Boy, F., Evans, C. J., Edden, R. A. E., Lawrence, A. D., Singh, K. D., Husain, M., & Sumner, P. (2011). Dorsolateral prefrontal γ-aminobutyric acid in men predicts individual differences in rash impulsivity. *Biological Psychiatry*, *70*, 866–872.

Broos, N., Diergaarde, L., Schoffelmeer, A. N., Pattij, T., & De Vries, T. J. (2012). Trait impulsive choice predicts resistance to extinction and propensity to relapse to cocaine seeking: A bidirectional investigation. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *37*(6), 1377–1386.

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., Baldwin, R. M., Schwartzman, A. N., Shelby, E. S., Smith, C. E., Kessler, R. M., & Zald, D. H. (2010). Dopaminergic network differences in human impulsivity. *Science*, *329*(5991), 532. https://doi.org/10.1126/science.1185778

Cannella, N., Cosa-Linan, A., Roscher, M., Takahashi, T. T., Vogler, N., Wängler, B., & Spanagel, R. (2017). [18F]-Fluorodeoxyglucose-positron emission tomography in rats with prolonged cocaine self-administration suggests potential brain biomarkers for addictive behavior. *Frontiers in Psychiatry*, *8*, 218.

Caprioli, D., Sawiak, S. J., Merlo, E., Theobald, D. E. H., Spoelder, M., Jupp, B., Voon, V., Carpenter, T. A., Everitt, B. J., Robbins, T. W., & Dalley, J. W. (2014). Gamma aminobutyric acidergic and neuronal structural markers in the nucleus accumbens core underlie Trait-like impulsive behavior. *Biological Psychiatry*, *75*, 115–123.

Carli, M., & Invernizzi, R. W. (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. *Frontiers in Neural Circuits*, *8*, 58.

CDC. (2020). Understanding the Epidemic | Drug Overdose | CDC. Injury Center.

Chamberlain, S. R., Stochl, J., Redden, S. A., & Grant, J. E. (2018). Latent traits of impulsivity and compulsivity: Toward dimensional psychiatry. *Psychological Medicine*, *48*, 810–821.

Chen, B. T., Yau, H. J., Hatch, C., Kusumoto-Yoshida, I., Cho, S. L., Hopf, F. W., & Bonci, A. (2013). Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature*, *496*, 359–362. https://doi.org/10.1038/nature12024

Chudasama, Y., Passetti, F., Rhodes, S. E. V., Lopian, D., Desai, A., & Robbins, T. W. (2003). Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: Differential effects on selectivity, impulsivity and compulsivity. *Behavioral Brain Research*, *146*, 105–119. https://doi.org/10.1016/j.bbr.2003.09.020

Clark, L., Robbins, T. W., Ersche, K. D., & Sahakian, B. J. (2006). Reflection impulsivity in current and former substance users. *Biological Psychiatry*, *60*(5), 515–522. https://doi.org/10.1016/j.biopsych.2005.11.007

Clarke, H. F., Dalley, J. W., Crofts, H. S., Robbins, T. W., & Roberts, A. C. (2004). Cognitive inflexibility after prefrontal serotonin depletion. *Science*, *304*, 878–880. https://doi.org/10.1126/science.1094987

Clavier, R. M., & Fibiger, H. C. (1977). On the role of ascending catecholaminergic projections in intracranial self-stimulation of the substantia nigra. *Brain Research*, *131*, 271–286. https://doi.org/10.1016/0006-8993(77)90520-0

Cocker, P. J., Rotge, J.-Y., Daniel, M.-L., Belin-Rauscent, A., & Belin, D. (2020). Impaired decision making following escalation of cocaine self-administration predicts vulnerability to relapse in rats. *Addiction Biology*, *25*(3), e12738. https://doi.org/10.1111/adb.12738

Cole, B. J., & Robbins, T. W. (1989). Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi on performance of a 5-choice serial reaction time task in rats: Implications for theories of selective attention and arousal. *Behavioral Brain Research*, *33*, 165–179.

Cornish, J. L., Duffy, P., & Kalivas, P. W. (1999). A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behavior. *Neuroscience*, *93*, 1359–1367. https://doi.org/10.1016/S0306-4522(99)00214-6

Cox, S. M. L., Yau, Y., Larcher, K., Durand, F., Kolivakis, T., Delaney, J. S., Dagher, A., Benkelfat, C., & Leyton, M. (2017). Cocaine cue-induced dopamine release in recreational cocaine users. *Scientific Reports*, *7*, 1–5.

Dalley, J. W., Everitt, B. J., & Robbins, T. W. (2011). Impulsivity, compulsivity, and top-down cognitive control. *Neuron*, *69*, 680–694. https://doi.org/10.1016/j.neuron.2011.01.020

Dalley, J. W., Fryer, T. D., Brichard, L., Robinson, E. S. J., Theobald, D. E. H., Laane, K., Pena, Y., Murphy, E. R., Shah, Y., Probst, K., Abakumova, I., Aigbirhio, F. I., Richards, H. K., Hong, Y., Baron, J.-C., Everitt, B. J., & Robbins, T. W. (2007). Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science*, *315*, 1267–1270. https://doi.org/10.1126/science.1137073

Dalley, J. W., & Robbins, T. W. (2017). Fractionating impulsivity: Neuropsychiatric implications. *Nature Reviews Neuroscience*, *18*, 158–171.

Dalley, J. W., & Roiser, J. P. (2012). Dopamine, serotonin and impulsivity. *Neuroscience*, *215*, 42–58. https://doi.org/10.1016/j.neuroscience.2012.03.065

Dalley, J. W., Theobald, D. E., Eagle, D. M., Passetti, F., & Robbins, T. W. (2002). Deficits in impulse control associated with tonically-elevated serotonergic function in rat prefrontal cortex. *Neuropsychopharmacology*, *26*, 716–728. https://doi.org/10.1016/S0893-133X(01)00412-2

Davis-Reyes, B. D., Campbell, V. M., Land, M. A., Chapman, H. L., Stafford, S. J., & Anastasio, N. C. (2019). Profile of cortical *N*-methyl-D-aspartate receptor subunit expression associates with inherent motor impulsivity in rats. *Biochemical Pharmacology*, *168*, 204–213.

Daw, N. D., Kakade, S., & Dayan, P. (2002). Opponent interactions between serotonin and dopamine. *Neural Networks*, *15*, 603–616.

de Jonge, J. C., Vinkers, C. H., Hulshoff Pol, H. E., & Marsman, A. (2017). GABAergic mechanisms in schizophrenia: Linking postmortem and in vivo studies. *Frontiers in Psychiatry*, *8*(AUG), 118.

de Laat, B., Weerasekera, A., Leurquin-Sterk, G., Bormans, G., Himmelreich, U., Casteels, C., & Van Laere, K. (2018). Glutamatergic biomarkers for cocaine addiction: A longitudinal study using MR spectroscopy and mGluR5 PET in self-administering rats. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *59*(6), 952–959.

Deroche-Gamonet, V., Belin, D., & Piazza, P. V. (2004). Evidence for addiction-like behavior in the rat. *Science*, *305*, 1014–1017. https://doi.org/10.1126/science.1099020

Di Ciano, C. P., & Everitt, B. J. (2001). Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behavior. *Neuropsychopharmacology*, *25*, 341–360. https://doi.org/10.1016/S0893-133X(01)00235-4

Di Ciano, C. P., & Everitt, B. J. (2003). Differential control over drug-seeking behavior by drug-associated conditioned reinforcers and discriminative stimuli predictive of drug availability. *Behavioral Neuroscience*, *117*, 952–960.

Di Ciano, C. P., & Everitt, B. J. (2004). Direct interactions between the basolateral amygdala and nucleus accumbens core underlie cocaine-seeking behavior by rats. *Journal of Neuroscience*, *24*, 7167–7173. https://doi.org/10.1523/JNEUROSCI.1581-04.2004

Diergaarde, L., Pattij, T., Poortvliet, I., Hogenboom, F., de Vries, W., Schoffelmeer, A. N. M., & De Vries, T. J. (2008). Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. *Biological Psychiatry*, *63*, 301–308.

Donnelly, N. A., Paulsen, O., Robbins, T. W., & Dalley, J. W. (2015). Ramping single unit activity in the medial prefrontal cortex and ventral striatum reflects the onset of waiting but not imminent impulsive actions. *The European Journal of Neuroscience*, *41*(12), 1524–1537. https://doi.org/10.1111/ejn.12895

Dunovan, K., Lynch, B., Molesworth, T., & Verstynen, T. (2015). Competing basal ganglia pathways determine the difference between stopping and deciding not to go. *Elife*, *4*, e08723. https://doi.org/10.7554/eLife.08723

Eagle, D. M., Baunez, C., Hutcheson, D. M., Lehmann, O., Shah, A. P., & Robbins, T. W. (2008). Stop-signal reaction-time task performance: Role of prefrontal cortex and subthalamic nucleus. *Cerebral Cortex*, *18*(1), 178–188. https://doi.org/10.1093/cercor/bhm044

Eagle, D. M., Lehmann, O., Theobald, D. E. H., Pena, Y., Zakaria, R., Ghosh, R., Dalley, J. W., & Robbins, T. W. (2009). Serotonin depletion impairs waiting but not stop-signal reaction time in rats: Implications for theories of the role of 5-HT in behavioral inhibition. *Neuropsychopharmacology*, *34*(5), 1311–1321. https://doi.org/10.1038/npp.2008.202

Eagle, D. M., Schepisi, C., Chugh, S., Desai, S., Han, S. Y. S., Huang, T., Lee, J. J., Sobala, C., Ye, W., Milton, A. L., & Robbins, T. W. (2020). Dissociable dopaminergic and pavlovian influences in goal-trackers and sign-trackers on a model of compulsive checking in OCD. *Psychopharmacology (Berl.)*, *237*, 3569–3581. https://doi.org/10.1007/s00213-020-05636-3

Eagle, D. M., Tufft, M. R. A., Goodchild, H. L., & Robbins, T. W. (2007). Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. *Psychopharmacology (Berl.)*, *192*, 193–206. https://doi.org/10.1007/s00213-007-0701-7

Eagle, D. M., Wong, J. C. K., Allan, M. E., Mar, A. C., Theobald, D. E., & Robbins, T. W. (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. *Journal of Neuroscience*, *31*, 7349–7356. https://doi.org/10.1523/JNEUROSCI.6182-10.2011

Economidou, D., Pelloux, Y., Robbins, T. W., Dalley, J. W., & Everitt, B. J. (2009). High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. *Biological Psychiatry*, *65*, 851–856.

Economidou, D., Theobald, D. E., Robbins, T. W., Everitt, B. J., & Dalley, J. W. (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. https://doi.org/10.1038/npp.2012.53

Ende, G., Cackowski, S., Van Eijk, J., Sack, M., Demirakca, T., Kleindienst, N., Bohus, M., Sobanski, E., Krause-Utz, A., & Schmahl, C. (2016). Impulsivity and aggression in female BPD and ADHD patients: Association with ACC glutamate and GABA concentrations. *Neuropsychopharmacology*, *41*(2), 410–418. https://doi.org/10.1038/npp.2015.153

Engeli, E. J. E., Zoelch, N., Hock, A., Nordt, C., Hulka, L. M., Kirschner, M., Scheidegger, M., Esposito, F., Baumgartner, M. R., Henning, A., & Seifritz, E. (2020). Impaired glutamate homeostasis in the nucleus accumbens in human cocaine addiction. *Molecular Psychiatry*, *25*, 1–9.

Erb, S., Hitchcott, P. K., Rajabi, H., Mueller, D., Shaham, Y., & Stewart, J. (2000). Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. *Neuropsychopharmacology*, *23*, 138–150. https://doi.org/10.1016/S0893-133X(99)00158-X

Ersche, K. D., Lim, T. V., Murley, A. G., Rua, C., Vaghi, M. M., White, T. L., Williams, G. B., & Robbins, T. W. (2020). Reduced glutamate turnover in the putamen is linked with automatic habits in human cocaine addiction. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2020.12.009

Ersche, K. D., Turton, A. J., Pradhan, S., Bullmore, E. T., & Robbins, T. W. (2010). Drug addiction endophenotypes: Impulsive versus sensation-seeking personality traits. *Biological Psychiatry*, *68*, 770–773.

España, R. A., Schmeichel, B. E., & Berridge, C. W. (2016). Norepinephrine at the nexus of arousal, motivation and relapse. *Brain Research*, *1641*, 207–216. https://doi.org/10.1016/j.brainres.2016.01.002

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology (Berl.)*, *146*, 348–361. https://doi.org/10.1007/PL00005481

Everitt, B. J. (2014). Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories - indications for novel treatments of addiction. *European Journal of Neuroscience*, *40*(1), 2163–2182. https://doi.org/10.1111/ejn.12644

Everitt, B. J., Belin, D., Economidou, D., Pelloux, Y., Dalley, J. W., & Robbins, T. W. (2008). Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *363*(1507), 3125–3135. https://doi.org/10.1098/rstb.2008.0089

Everitt, B. J., & Robbins, T. W. (2016). Drug addiction: Updating actions to habits to compulsions ten years on. *Annual Review of Psychology*, *67*, 23–50. https://doi.org/10.1146/annurev-psych-122414-033457

Feola, T. W., Wit, H., & De, R. J. B. (2000). Effects of d-amphetamine and alcohol on a measure of behavioral inhibition in rats. *Behavioral Neuroscience*, *114*, 838–848.

Fineberg, N. A., Chamberlain, S. R., Goudriaan, A. E., Stein, D. J., Vanderschuren, L. J. M. J., Gillan, C. M., Shekar, S., Gorwood, P. A. P. M., Voon, V., Morein-Zamir, S., Denys, D., Sahakian, B. J., Moeller, F. G., Robbins, T. W., & Potenza, M. N. (2014). New developments in human neurocognition: Clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. *CNS Spectrums*, *19*, 69–89. https://doi.org/10.1017/S1092852913000801

Fineberg, N. A., Potenza, M. N., Chamberlain, S. R., Berlin, H. A., Menzies, L., Bechara, A., Sahakian, B. J., Robbins, T. W., Bullmore, E. T., & Hollander, E. (2010). Probing compulsive and impulsive behaviors, from animal models to endophenotypes: A narrative review. *Neuropsychopharmacology*, *35*(3), 591–604. https://doi.org/10.1038/npp.2009.185

Fink, L. H. L., Anastasio, N. C., Fox, R. G., Rice, K. C., Moeller, F. G., & Cunningham, K. A. (2015). Individual differences in impulsive action reflect variation in the cortical serotonin 5-HT2A receptor system. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *40*(8), 1957–1968. https://doi.org/10.1038/npp.2015.46

Floresco, S. B., Tse, M. T. L., & Ghods-Sharifi, S. (2008). Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology*, *33*, 1966–1979. https://doi.org/10.1038/sj.npp.1301565

Giuliano, C., Belin, D., & Everitt, B. J. (2019). Compulsive alcohol seeking results from a failure to disengage dorsolateral striatal control over behavior. *Journal of Neuroscience*, *39*, 1744–1754.

Grassi, G., Laura, M., Lorenzo, D. C. M., Elisa, C., Lorenzo, R., Carla, G., & Stefano, P. (2016). Atomoxetine for hoarding disorder: A pre-clinical and clinical investigation. *Journal of Psychiatric Research*, *83*, 240–248. https://doi.org/10.1016/j.jpsychires.2016.09.012

Greenwell, T. N., Walker, B. M., Cottone, P., Zorrilla, E. P., & Koob, G. F. (2009). The α1 adrenergic receptor antagonist prazosin reduces heroin self-administration in rats with extended access to heroin administration. *Pharmacology, Biochemistry and Behavior*, *91*, 295–302.

Groman, S. M., Hillmer, A. T., Liu, H., Fowles, K., Holden, D., Morris, E. D., Lee, D., & Taylor, J. R. (2020). Dysregulation of decision making related to metabotropic glutamate 5, but not midbrain D3, receptor availability following cocaine self-administration in rats. *Biological Psychiatry*, *88*, 777–787.

Groman, S. M., James, A. S., Seu, E., Crawford, M. A., Harpster, S. N., & Jentsch, J. D. (2013). Monoamine levels within the orbitofrontal cortex and putamen interact to predict reversal learning performance. *Biological Psychiatry*, *73*, 756–762.

Groman, S. M., Lee, B., London, E. D., Mandelkern, M. A., James, A. S., Feiler, K., Rivera, R., Dahlbom, M., Sossi, V., Vandervoort, E., & Jentsch, J. D. (2011). Dorsal striatal D2-like receptor availability covaries with sensitivity to positive reinforcement during discrimination learning. *Journal of Neuroscience*, *31*, 7291–7299. https://doi.org/10.1523/JNEUROSCI.0363-11.2011

Haber, S. N., Fudge, J. L., & McFarland, N. R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *Journal of Neuroscience*, *20*, 2369–2382. https://doi.org/10.1523/JNEUROSCI.20-06-02369.2000

Harrison, A. A., Everitt, B. J., & Robbins, T. W. (1997). Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: Interactions with dopaminergic mechanisms. *Psychopharmacology*, *133*(4), 329–342. https://doi.org/10.1007/s002130050410

Harrison, A. A., Everitt, B. J., & Robbins, T. W. (1999). Central serotonin depletion impairs both the acquisition and performance of a symmetrically reinforced go/no-go conditional visual discrimination. *Behavioral Brain Research*, *100*, 99–112.

Hausknecht, K. A., San George, M., Gancarz, A. M., Ashrafioun, L., De Wit, H., Zhuang, Z., & Richards, J. B. (2006). Impulsivity in serotonin transporter knock-out mice: Effects of methylphenidate. Program No. 749.8/Y12 2006 Neuroscience Meeting Planner, Society for Neuroscience, Atlanta, GA.

Hervé, D., Pickel, V. M., Joh, T. H., & Beaudet, A. (1987). Serotonin axon terminals in the ventral tegmental area of the rat: Fine structure and synaptic input to dopaminergic neurons. *Brain Research*, *435*, 71–83. https://doi.org/10.1016/0006-8993(87)91588-5

Higgins, G. A., Brown, M., St, J. J., MacMillan, C., Silenieks, L. B., & Thevarkunnel, S. (2020). Effects of 5-HT2C receptor modulation and the NA reuptake inhibitor atomoxetine in tests of compulsive and impulsive behaviour. *Neuropharmacology*, *170*, 108064. https://doi.org/10.1016/j.neuropharm.2020.108064

Higgins, G. A., Silenieks, L. B., Altherr, E. B., MacMillan, C., Fletcher, P. J., & Pratt, W. E. (2016). Lorcaserin and CP-809101 reduce motor impulsivity and reinstatement of food seeking behavior in male rats: Implications for understanding the anti-obesity property of 5-HT2C receptor agonists. *Psychopharmacology (Berl).*, *233*, 2841–2856. https://doi.org/10.1007/s00213-016-4329-3

Hopf, F. W., Chang, S.-J., Sparta, D. R., Bowers, M. S., & Bonci, A. (2010). Motivation for alcohol becomes resistant to quinine adulteration after 3–4 months of intermittent alcohol self-administration. *Alcoholism, Clinical and Experimental Research*, *34*(9), 1565–1573.

Hopf, F. W., & Lesscher, H. M. B. (2014). Rodent models for compulsive alcohol intake. *Alcohol (Fayetteville, N.Y.)*, *48*(3), 253–264. https://doi.org/10.1016/j.alcohol.2014.03.001

Howell, L. L., & Cunningham, K. A. (2015). Serotonin 5-HT2 receptor interactions with dopamine function: Implications for therapeutics in cocaine use disorder. *Pharmacological Reviews*, *67*(1), 176–197.

Hu, Y., Salmeron, B. J., Gu, H., Stein, E. A., & Yang, Y. (2015). Impaired functional connectivity within and between frontostriatal circuits and its association with compulsive drug use and trait impulsivity in cocaine addiction. *JAMA Psychiatry*, *72*(6), 584–592. https://doi.org/10.1001/jamapsychiatry.2015.1

Hu, Y., Salmeron, B. J., Krasnova, I. N., Gu, H., Lu, H., Bonci, A., Cadet, J. L., Stein, E. A., & Yang, Y. (2019). Compulsive drug use is associated with imbalance of orbitofrontal- and prelimbic-striatal circuits in punishment-resistant individuals. *Proceedings of the National Academy of Sciences*, *116*(18), 9066–9071. https://doi.org/10.1073/pnas.1819978116

Hyman, S. E. (2005). Addiction: A disease of learning and memory. *American Journal of Psychiatry*, *162*, 1414–1422.

Ikemoto, S. (2007). Dopamine reward circuitry: Two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Research Reviews*, *56*, 27–78. https://doi.org/10.1016/j.brainresrev.2007.05.004

Ito, R., Dalley, J. W., Robbins, T. W., & Everitt, B. J. (2002). Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *Journal of Neuroscience*, *22*, 6247–6253. https://doi.org/10.1523/JNEUROSCI.22-14-06247.2002

Izquierdo, A. (2017). Functional heterogeneity within rat orbitofrontal cortex in reward learning and decision making. *Journal of Neuroscience*, *37*, 10529–10540. https://doi.org/10.1523/JNEUROSCI.1678-17.2017

Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl).*, *146*, 373–390. https://doi.org/10.1007/PL00005483

Jupp, B., Caprioli, D., Saigal, N., Reverte, I., Shrestha, S., Cumming, P., Everitt, B. J., Robbins, T. W., & Dalley, J. W. (2013). Dopaminergic and GABA-ergic markers of impulsivity in rats: Evidence for anatomical localisation in ventral striatum and prefrontal cortex. *European Journal of Neuroscience*, *37*, 1519–1528.

Kalivas, P. W. (2009). The glutamate homeostasis hypothesis of addiction. *Nature Reviews Neuroscience*, *10*, 561–572.

Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: A pathology of motivation and choice. *American Journal of Psychiatry*, *162*, 1403–1413.

Kapur, S., & Remington, G. (1996). Serotonin-dopamine interaction and its relevance to schizophrenia. *American Journal of Psychiatry*, *153*, 466–476.

Kasanetz, F., Deroche-Gamonet, V., Berson, N., Balado, E., Lafourcade, M., Manzoni, O., & Vincenzo, P. P. (2010). Transition to addiction is associated with a persistent impairment in synaptic plasticity. *Science*, *328*, 1709–1712. https://doi.org/10.1126/science.1187801

Kasanetz, F., Lafourcade, M., Deroche-Gamonet, V., Revest, J. M., Berson, N., Balado, E., Fiancette, J. F., Renault, P., Piazza, P. V., & Manzoni, O. J. (2013). Prefrontal synaptic markers of cocaine addiction-like behavior in rats. *Molecular Psychiatry*, *18*, 729–737.

Koob, G. F. (2009). Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology*, *56*(Suppl 1), 18–31. https://doi.org/10.1016/j.neuropharm.2008.07.043

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet. Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

LaLumiere, R. T., & Kalivas, P. W. (2008). Glutamate release in the nucleus accumbens core is necessary for heroin seeking. *Journal of Neuroscience*, *28*, 3170–3177. https://doi.org/10.1523/JNEUROSCI.5129-07.2008

Lee, B., Tiefenbacher, S., Platt, D. M., & Spealman, R. D. (2004). Pharmacological blockade of α2-adrenoceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. *Neuropsychopharmacology*, *29*, 686–693. https://doi.org/10.1038/sj.npp.1300391

Leon, D. A., Saburova, L., Tomkins, S., Andreev, E., Kiryanov, N., McKee, M., & Shkolnikov, V. M. (2007). Hazardous alcohol drinking and premature mortality in Russia: A population based case-control study. *Lancet (London, England)*, *369*(9578), 2001–2009.

Letchworth, S. R., Nader, M. A., Smith, H. R., Friedman, D. P., & Porrino, L. J. (2001). Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys. *Journal of Neuroscience*, *21*, 2799–2807. https://doi.org/10.1523/JNEUROSCI.21-08-02799.2001

Li, J. N., Liu, X. L., & Li, L. (2020). Prefrontal GABA and glutamate levels correlate with impulsivity and cognitive function of prescription opioid addicts: A 1H-magnetic resonance spectroscopy study. *Psychiatry and Clinical Neurosciences*, *74*(1), 77–83.

Li, Y., Zhang, C. C., Weidacker, K., Zhang, Y., He, N., Jin, H., Chen, W., Voon, V., Edden, R. A. E., & Yan, F. (2019) Investigation of anterior cingulate cortex gamma-aminobutyric acid and glutamate-glutamine levels in obsessive-compulsive disorder using magnetic resonance spectroscopy. *BMC Psychiatry*, *19*, 1–9.

Liley, A. E., Gabriel, D. B. K., Sable, H. J., & Simon, N. W. (2019). Sex differences and effects of predictive cues on delayed punishment discounting. *Eneuro*, *6*(4), ENEURO.0225-19.2019. https://doi.org/10.1523/ENEURO.0225-19.2019

Loos, M., Pattij, T., Janssen, M. C. W., Counotte, D. S., Schoffelmeer, A. N. M., Smit, A. B., Spijker, S., & van Gaalen, M. M. (2010). Dopamine receptor D1/D5 gene expression in the medial prefrontal cortex predicts impulsive choice in rats. *Cerebral Cortex*, *20*, 1064–1070.

López-Grancha, M., Lopez-Crespo, G., Sanchez-Amate, M. C., & Flores, P. (2008). Individual differences in schedule-induced polydipsia and the role of gabaergic and dopaminergic systems. *Psychopharmacology (Berl).*, *197*, 487–498.

Lüscher, C., Robbins, T. W., & Everitt, B. J. (2020). The transition to compulsion in addiction. *Nature Reviews Neuroscience*, *21*, 247–263.

Lustberg, D., Tillage, R., Bai, Y., Pruitt, M., Liles, L. C., & Weinshenker, D. (2020). Noradrenergic circuits in the forebrain control affective responses to novelty. *Psychopharmacology (Berl)*, *237*(11), 3337–3355.

Maccioni, P., Pes, D., Fantini, N., Carai, M. A. M., Gessa, G. L., & Colombo, G. (2008). γ-Hydroxybutyric acid (GHB) suppresses alcohol's motivational properties in alcohol-preferring rats. *Alcohol*, *42*, 107–113. https://doi.org/10.1016/j.alcohol.2008.01.001

Mamiya, T., Tanase, S., Takeuchi, S., Kato, S., Ito, A., Hiramatsu, M., & Nabeshima, T. (2020). Galantamine improves enhanced impulsivity, impairments of attention and long-term potentiation induced by prenatal nicotine exposure to mice. *Biochemical Pharmacology*, *180*, 114139.

Mantsch, J. R., Weyer, A., Vranjkovic, O., Beyer, C. E., Baker, D. A., & Caretta, H. (2010). Involvement of noradrenergic neurotransmission in the stress- but not cocaine-induced reinstatement of extinguished cocaine-induced conditioned place preference in mice: Role for β-2 adrenergic receptors. *Neuropsychopharmacology*, *35*, 2165–2178. https://doi.org/10.1038/npp.2010.86

Marchant, N. J., & Kaganovsky, K. (2015). A critical role of nucleus accumbens dopamine D1-family receptors in renewal of alcohol seeking after punishment-imposed abstinence. *Behavioral Neuroscience*, *129*, 281–291.

Miyazaki, K., Miyazaki, K. W., Sivori, G., Yamanaka, A., Tanaka, K. F., & Doya, K. (2020). Serotonergic projections to the orbitofrontal and medial prefrontal cortices differentially modulate waiting for future rewards. *Science Advances*, *6*, eabc7246.

Miyazaki, K. W., Miyazaki, K., Tanaka, K. F., Yamanaka, A., Takahashi, A., Tabuchi, S., & Doya, K. (2014). Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards. *Current Biology*, *24*, 2033–2040.

Mobini, S., Chiang, T. J., Al-Ruwaitea, A. S. A., Ho, M. Y., Bradshaw, C. M., & Szabadi, E. (2000). Effect of central 5-hydroxytryptamine depletion on inter-temporal choice: A quantitative analysis. *Psychopharmacology (Berl)*, *149*(3), 313–318.

Mora, S., Merchán, A., Vilchez, O., Aznar, S., Klein, A. B., Ultved, L., Campa, L., Suñol, C., Flores, P., & Moreno, M. (2018). Reduced cortical serotonin 5-HT2A receptor binding and glutamate activity in high compulsive drinker rats. *Neuropharmacology*, *143*, 10–19. https://doi.org/10.1016/j.neuropharm.2018.09.004

Müller, C. P., & Homberg, J. R. (2015). The role of serotonin in drug use and addiction. *Behavioural Brain Research*, *277*, 146–192. https://doi.org/10.1016/j.bbr.2014.04.007

Murley, A. G., Rouse, M. A., Jones, P. S., Ye, R., Hezemans, F. H., O'Callaghan, C., Frangou, P., Kourtzi, Z., Rua, C., Carpenter, T. A., Rodgers, C. T., & Rowe, J. B. (2020). GABA and glutamate deficits from frontotemporal lobar degeneration are associated with disinhibition. *Brain*, *143*(11), 3449–3462. https://doi.org/10.1093/brain/awaa305

Murphy, E. R., Dalley, J. W., & Robbins, T. W. (2005). Local glutamate receptor antagonism in the rat prefrontal cortex disrupts response inhibition in a visuospatial attentional task. *Psychopharmacology (Berl).*, *179*, 99–107. https://doi.org/10.1007/s00213-004-2068-3

Murphy, E. R., Fernando, A. B. P., Urcelay, G. P., Robinson, E. S. J., Mar, A. C., Theobald, D. E. H., Dalley, J. W., & Robbins, T. W. (2012). Impulsive behaviour induced by both NMDA receptor antagonism and GABA A receptor activation in rat ventromedial prefrontal cortex. *Psychopharmacology*, *219*(2), 401–410. https://doi.org/10.1007/s00213-011-2572-1

Murphy, J. G., Vuchinich, R. E., & Simpson, C. A. (2001). Delayed reward and cost discounting. *The Psychological Record*, *51*(4), 571–588.

Murray, J. E., Belin, D., & Everitt, B. J. (2012). Double dissociation of the dorsomedial and dorsolateral striatal control over the acquisition and performance of cocaine seeking. *Neuropsychopharmacology*, *37*, 2456–2466. https://doi.org/10.1038/npp.2012.104

Nader, M. A., Daunais, J. B., Moore, T., Nader, S. H., Moore, R. J., Smith, H. R., Friedman, D. P., & Porrino, L. J. (2002). Effects of cocaine self-administration on striatal dopamine systems in rhesus monkeys: Initial and chronic exposure. *Neuropsychopharmacology*, *27*, 35–46. https://doi.org/10.1016/S0893-133X(01)00427-4

Navarro, S. V., Gutiérrez-Ferre, V., Flores, P., & Moreno, M. (2015). Activation of serotonin 5-HT2A receptors inhibits high compulsive drinking on schedule-induced polydipsia. *Psychopharmacology (Berl).*, *232*, 383–397. https://doi.org/10.1007/s00213-014-3699-7

Nocjar, C., Alex, K. D., Sonneborn, A., Abbas, A. I., Roth, B. L., & Pehek, E. A. (2015). Serotonin-2C and -2a receptor co-expression on cells in the rat medial prefrontal cortex. *Neuroscience*, *297*, 22–37. https://doi.org/10.1016/j.neuroscience.2015.03.050

Orsini, C. A., Blaes, S. L., Dragone, R. J., Betzhold, S. M., Finner, A. M., Bizon, J. L., & Setlow, B. (2020). Distinct relationships between risky decision making and cocaine self-administration under short- and long-access conditions. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *98*, 109791.

Orsini, C. A., Blaes, S. L., Setlow, B., & Simon, N. W. (2019). Recent updates in modeling risky decision making in rodents. *Methods in Molecular Biology (Clifton, N.J.)*, *2011*, 79–92.

Page, C. E., Alexander, J., Shepard, R., & Coutellier, L. (2018). Npas4 deficiency interacts with adolescent stress to disrupt prefrontal GABAergic maturation and adult cognitive flexibility. *Genes, Brain and Behavior*, *17*(6), e12459.

Paine, T. A., Cooke, E. K., & Lowes, D. C. (2015). Effects of chronic inhibition of GABA synthesis on attention and impulse control. *Pharmacology, Biochemistry and Behavior*, *135*, 97–104.

Parsons, L. H., Koob, G. F., & Weiss, F. (1995). Serotonin dysfunction in the nucleus accumbens of rats during withdrawal after unlimited access to intravenous cocaine. *Journal of Pharmacology and Experimental Therapeutics*, *274*(3), 1182–1191.

Patkina, N. A., & Lapin, I. P. (1976). Effect of serotoninergic drugs on positive and negative reinforcing systems in cats. *Pharmacology, Biochemistry and Behavior*, *5*(3), 241–245. https://doi.org/10.1016/0091-3057(76)90073-3

Pattij, T., Janssen, M. C. W., Vanderschuren, L. J. M. J., Schoffelmeer, A. N. M., & van Gaalen, M. M. (2007). Involvement of dopamine D1 and D2 receptors in the nucleus accumbens core and shell in inhibitory response control. *Psychopharmacology (Berl).*, *191*, 587–598. https://doi.org/10.1007/s00213-006-0533-x

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*, 768–774.

Pellon, R., & Blackman, D. E. (1992). Effects of drugs on the temporal distribution of schedule-induced polydipsia in rats. *Pharmacology, Biochemistry and Behavior*, *43*, 689–695.

Pelloux, Y., Dilleen, R., Economidou, D., Theobald, D., & Everitt, B. J. (2012). Reduced forebrain serotonin transmission is causally involved in the development of compulsive cocaine seeking in rats. *Neuropsychopharmacology*, *37*, 2505–2514. https://doi.org/10.1038/npp.2012.111

Perry, J. L., Larson, E. B., German, J. P., Madden, G. J., & Carroll, M. E. (2005). Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. *Psychopharmacology (Berl).*, *178*, 193–201. https://doi.org/10.1007/s00213-004-1994-4

Pezze, M. A., Dalley, J. W., & Robbins, T. W. (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 (Berl).*, *202*, 307–313. https://doi.org/10.1007/s00213-008-1384-4

Piantadosi, P. T., Yeates, D. C. M., & Floresco, S. B. (2020). Prefrontal cortical and nucleus accumbens contributions to discriminative conditioned suppression of reward-seeking. *Learn. Mem.*, *27*, 429–440.

Piazza, P. V., Mittleman, G., Deminie`re, J. M., Le Moal, M., & Simon, H. (1993). Relationship between schedule-induced polydipsia and amphetamine intravenous self-administration. Individual differences and role of experience. *Behavioural Brain Research*, *55*(2), 185–193.

Pisansky, M. T., Lefevre, E. M., Retzlaff, C. L., Trieu, B. H., Leipold, D. W., & Rothwell, P. E. (2019). Nucleus accumbens fast-spiking interneurons constrain impulsive action. *Biological Psychiatry*, *86*, 836–847.

Porrino, L. J., Lyons, D., Smith, H. R., Daunais, J. B., & Nader, M. A. (2004). Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. *Journal of Neuroscience*, *24*, 3554–3562. https://doi.org/10.1523/JNEUROSCI.5578-03.2004

Prados-Pardo, Á., Martín-González, E., Mora, S., Merchán, A., Flores, P., & Moreno, M. (2019). Increased fear memory and glutamatergic modulation in compulsive drinker rats selected by schedule-induced polydipsia. *Frontiers in Behavioral Neuroscience*, *13*, 100.

Puumala, T., & Sirviö, J. (1998). Changes in activities of dopamine and serotonin systems in the frontal cortex underlie poor choice accuracy and impulsivity of rats in an attention task. *Neuroscience*, *83*, 489–499. https://doi.org/10.1016/S0306-4522(97)00392-8

Radke, A. K., Nakazawa, K., & Holmes, A. (2015). Cortical GluN2B deletion attenuates punished suppression of food reward-seeking. *Psychopharmacology (Berl).*, *232*, 3753–3761. https://doi.org/10.1007/s00213-015-4033-8

Reichel, J. M., Nissel, S., Rogel-Salazar, G., Mederer, A., KÃ¤fer, K., Bedenk, B. T., Martens, H., Anders, R., Grosche, J., Michalski, D., HÃ¤rtig, W., & Wotjak, C. T. (2015). Distinct behavioral consequences of short-term and prolonged GABAergic depletion in prefrontal cortex and dorsal hippocampus. *Frontiers in Behavioral Neuroscience*, *8*, 452.

Robbins, T. W., Gillan, C. M., Smith, D. G., de Wit, S., & Ersche, K. D. (2012). Neurocognitive endophenotypes of impulsivity and compulsivity: Towards dimensional psychiatry. *Trends in Cognitive Sciences*, *16*, 81–91.

Roberto, M., Madamba, S. G., Stouffer, D. G., Parsons, L. H., & Siggins, G. R. (2004). Increased GABA release in the central amygdala of ethanol-dependent rats. *Journal of Neuroscience*, *24*(45), 10159–10166.

Robinson, E. S. J., Dalley, J. W., Theobald, D. E., Glennon, J. C., Pezze, M. A., Murphy, E. R., & Robbins, T. W. (2008). Opposing roles for 5-HT2A and 5-HT2C receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. *Neuropsychopharmacology*, *33*(10), 2398–2406.

Robinson, E. S. J., Eagle, D. M., Mar, A. C., Bari, A., Banerjee, G., Jiang, X., Dalley, J. W., & Robbins, T. W. (2008). Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. *Neuropsychopharmacology*, *33*(5), 1028–1037. https://doi.org/10.1038/sj.npp.1301487

Saunders, B. T., Yager, L. M., & Robinson, T. E. (2013). Cue-evoked cocaine "craving": Role of dopamine in the accumbens core. *Journal of Neuroscience*, *33*, 13989–14000.

Sawiak, S. J., Jupp, B., Taylor, T., Caprioli, D., Carpenter, T. A., & Dalley, J. W. (2016). In vivo γ-aminobutyric acid measurement in rats with spectral editing at 4.7T. *Journal of Magnetic Resonance Imaging*, *43*, 1308–1312.

Seif, T., Chang, S.-J., Simms, J. A., Gibb, S. L., Dadgar, J., Chen, B. T., Harvey, B. K., Ron, D., Messing, R. O., Bonci, A., & Hopf, F. W. (2013). Cortical activation of accumbens hyperpolarization-active NMDARs mediates aversion-resistant alcohol intake. *Nature Neuroscience*, *16*(8), 1094–1100. https://doi.org/10.1038/nn.3445

Siciliano, C. A., Noamany, H., Chang, C. J., Brown, A. R., Chen, X., Leible, D., Lee, J. J., Wang, J., Vernon, A. N., Vander Weele, C. M., & Kimchi, E. Y. (2019). A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. *Science*, *366*, 1008–1012.

Simon, N. W., Gilbert, R. J., Mayse, J. D., Bizon, J. L., & Setlow, B. (2009). Balancing risk and reward: A rat model of risky decision-making. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *34*(10), 2208–2217.

Smith, R. J., & Aston-Jones, G. (2011). α 2 Adrenergic and imidazoline receptor agonists prevent cue-induced cocaine seeking. *Biological Psychiatry*, *70*, 712–719.

Solecki, W. B., Szklarczyk, K., Pradel, K., Kwiatkowska, K., Dobrzański, G., & Przewłocki, R. (2018). Noradrenergic signaling in the VTA modulates cocaine craving. *Addiction Biology*, *23*, 596–609.

Soubrié, P. (1986). Reconciling the role of central serotonin neurons in human and animal behavior. *The Behavioral and Brain Sciences*, *9*, 319–335. https://doi.org/10.1017/S0140525X00022871

Soubrie, P., Thiebot, M. H., Jobert, A., & Hamon, M. (1981). Serotoninergic control of punished behavior: Effects of intra-raphe microinjections of chlordiazepoxide, GABA and 5-HT on behavioral suppression in rats. *Journal De Physiologie*, *77*(2-3), 449–453.

Spano, M. S., Ellgren, M., Wang, X., & Hurd, Y. L. (2007). Prenatal cannabis exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood. *Biological Psychiatry*, *61*, 554–563.

Sun, W. L., & Yuill, M. B. (2020). Role of the GABAa and GABAb receptors of the central nucleus of the amygdala in compulsive cocaine-seeking behavior in male rats. *Psychopharmacology (Berl).*, *237*, 3759–3771.

Tedford, S. E., Persons, A. L., & Napier, T. C. (2015). Dopaminergic lesions of the dorsolateral striatum in rats increase delay discounting in an impulsive choice task. *PLoS One*, *10*, e0122063.

Terra, H., Bruinsma, B., de Kloet, S. F., van der Roest M., Pattij, T., & Mansvelder, H. D. (2020). Prefrontal cortical projection neurons targeting dorsomedial striatum control behavioral inhibition. *Current Biology*, *30*, 4188–4200.e5.

Thiébot, M. H., Hamon, M., & Soubrié, P. (1983). The involvement of nigral serotonin innervation in the control of punishment-induced behavioral inhibition in rats. *Pharmacology, Biochemistry and Behavior*, *19*, 225–229.

Tiego, J., Chamberlain, S. R., Harrison, B. J., Dawson, A., Albertella, L., Youssef, G. J., Fontenelle, L. F., & Yücel, M. (2020). Heritability of overlapping impulsivity and compulsivity dimensional phenotypes. *Scientific Reports*, *10*, 14378.

Tyacke, R. J., Lingford-Hughes, A., Reed, L. J., & Nutt, D. J. (2010). GABA B receptors in addiction and its treatment. *Advances in Pharmacology*, *58*, 373–396.

Ucha, M., Roura-Martínez, D., Contreras, A., Pinto-Rivero, S., Orihuel, J., Ambrosio, E., & Higuera-Matas, A. (2019). Impulsive action and impulsive choice are differentially associated with gene expression variations of the GABAA receptor alfa 1 subunit and the CB1 receptor in the lateral and medial orbitofrontal cortices. *Frontiers in Behavioral Neuroscience*, *13*, 22.

UNODC. (2020). UNODC World Drug Report 2020: Global drug use rising; while COVID-19 has far reaching impact on global drug markets.

van Gaalen, M. M., van Koten, R., Schoffelmeer, A. N. M., Louk, J. M. J., & Vanderschuren, L. J. M. J. (2006). Critical involvement of dopaminergic neurotransmission in impulsive decision making. *Biological Psychiatry*, *60*(1), 66–73. https://doi.org/10.1016/j.biopsych.2005.06.005

van Huijstee, A. N., & Mansvelder, H. D. (2015). Glutamatergic synaptic plasticity in the mesocorticolimbic system in addiction. *Frontiers in Cellular Neuroscience*, *8*(JAN), 1–13. https://doi.org/10.3389/fncel.2014.00466

Vanderschuren, L. J. M. J., Di Ciano, P., & Everitt, B. J. (2005). Involvement of the dorsal striatum in cue-controlled cocaine seeking. *Journal of Neuroscience*, *25*, 8665–8670. https://doi.org/10.1523/JNEUROSCI.0925-05.2005

Vanderschuren, L. J. M. J., & Everitt, B. J. (2005). Behavioral and neural mechanisms of compulsive drug seeking. *European Journal of Pharmacology*, *526*(1–3), 77–88. https://doi.org/10.1016/j.ejphar.2005.09.037

Vengeliene, V., Roßmanith, M., Takahashi, T. T., Alberati, D., Behl, B., Bespalov, A., & Spanagel, R. (2018). Targeting glycine reuptake in alcohol seeking and relapse. *Journal of Pharmacology and Experimental Therapeutics*, *365*, 202–211.

Verdejo-Garcia, A., & Albein-Urios, N. (2021). Impulsivity traits and neurocognitive mechanisms conferring vulnerability to substance use disorders. *Neuropharmacology*, *183*, 108402.

Verdejo-García, A., Lawrence, A. J., & 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. *Neuroscience and Biobehavioral Reviews*, *32*, 777–810.

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Ding, Y. S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C., & Pappas, N. (2001). Low level of brain dopamine D2 receptors in methamphetamine abusers: Association with metabolism in the orbitofrontal cortex. *The American Journal of Psychiatry*, *158*(12), 2015–2021.

Volkow, N. D., Fowler, J. S., Wang, G. J., Hitzemann, R., Logan, J., Schlyer, D. J., Dewey, S. L., & Wolf, A. P. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse (New York. N.Y.)*, *14*(2), 169–177.

Wang, J., Lanfranco, M. F., Gibb, S. L., Yowell, Q. V., Carnicella, S., & Ron, D. (2010). Long-lasting adaptations of the NR2B-containing NMDA receptors in the dorsomedial striatum play a crucial role in alcohol consumption and relapse. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(30), 10187–10198. https://doi.org/10.1523/JNEUROSCI.2268-10.2010

Weafer, J., Mitchell, S. H., & de Wit, H. (2014). Recent translational findings on impulsivity in relation to drug abuse. *Current Addiction Reports*, *1*, 289–300.

Wee, S., Mandyam, C. D., Lekic, D. M., & Koob, G. F. (2008). α1-Noradrenergic system role in increased motivation for cocaine intake in rats with prolonged access. *European Neuropsychopharmacology*, *18*, 303–311. https://doi.org/10.1016/j.euroneuro.2007.08.003

Weidacker, K., Johnston, S. J., Mullins, P. G., Boy, F., & Dymond, S. (2020). Impulsive decision-making and gambling severity: The influence of γ-amino-butyric acid (GABA) and glutamate-glutamine (Glx). *European Neuropsychopharmacology*, *32*, 36–46. https://doi.org/10.1016/j.euroneuro.2019.12.110

Weinshenker, D., & Schroeder, J. P. (2007). There and back again: A tale of norepinephrine and drug addiction. *Neuropsychopharmacology*, *32*, 1433–1451. https://doi.org/10.1038/sj.npp.1301263

Whelan, R., Conrod, P. J., Poline, J. B., Lourdusamy, A., Banaschewski, T., Barker, G. J., Bellgrove, M. A., Büchel, C., Byrne, M., Cummins, T. D., & Fauth-Bühler, M. (2012). Adolescent impulsivity phenotypes characterized by distinct brain networks. *Nature Neuroscience*, *15*, 920–925.

Whiteside, S. P., & Lynam, D. R. (2001). The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. *Personality and Individual Differences*, *30*, 669–689.

Willuhn, I., Burgeno, L. M., Everitt, B. J., & Phillips, P. E. M. (2012). Hierarchical recruitment of phasic dopamine signaling in the striatum during the progression of cocaine use. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 20703–20708.

Wilson, J. M., Kalasinsky, K. S., Levey, A. I., Bergeron, C., Reiber, G., Anthony, R. M., Schmunk, G. A., Shannak, K., Haycock, J. W., & Kish, S. J. (1996). Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nature Medicine*, *2*, 699–703.

Winstanley, C. A., Baunez, C., Theobald, D. E. H., & Robbins, T. W. (2005). Lesions to the subthalamic nucleus decrease impulsive choice but impair autoshaping in rats: The importance of the basal ganglia in Pavlovian conditioning and impulse control. *European Journal of Neuroscience*, *21*, 3107–3116.

Winstanley, C. A., Dalley, J. W., Theobald, D. E. H., & Robbins, T. W. (2003). Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology (Berl).*, *170*, 320–331.

Winstanley, C. A., Eagle, D. M., & Robbins, T. W. (2006). Behavioral models of impulsivity in relation to ADHD: Translation between clinical and preclinical studies. *Clinical Psychology Review*, *26*(4), 379–395.

Winstanley, C. A., Theobald, D. E. H., Cardinal, R. N., & Robbins, T. W. (2004). Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *24*(20), 4718–4722.

Winstanley, C. A., Theobald, D. E. H., Dalley, J. W., Glennon, J. C., & Robbins, T. W. (2004). 5-HT2A and 5-HT2C receptor antagonists

have opposing effects on a measure of impulsivity: Interactions with global 5-HT depletion. *Psychopharmacology (Berl).*, *176*, 376–385.

Wolffgramm, J., & Heyne, A. (1991). Social behavior, dominance, and social deprivation of rats determine drug choice. *Pharmacology, Biochemistry, and Behavior*, *38*(2), 389–399. https://doi.org/10.1016/0091-3057(91)90297-F

Yates, J. R. (2019). Examining the neurochemical underpinnings of animal models of risky choice: Methodological and analytic considerations. *Experimental and Clinical Psychopharmacology*, *27*(2), 178–201. https://doi.org/10.1037/pha0000239

Yates, J. R., & Bardo, M. T. (2017). Effects of intra-accumbal administration of dopamine and ionotropic glutamate receptor drugs on delay discounting performance in rats. *Behavioral Neuroscience*, *131*, 392–405.

Zhou, Z., Karlsson, C., Liang, T., Xiong, W., Kimura, M., Tapocik, J. D., Yuan, Q., Barbier, E., Feng, A., Flanigan, M., & Augier, E. (2013). Loss of metabotropic glutamate receptor 2 escalates alcohol consumption. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 16963–16968.

Zorrilla, E. P., & Koob, G. F. (2019). Impulsivity derived from the dark side: Neurocircuits that contribute to negative urgency. *Frontiers in Behavioural Neurosciences*, *13*, 136.

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