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REVIEW

Convergent pharmacological mechanisms in impulsivity and addiction: insights from rodent models

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Research over the last two decades has widely demonstrated that impulsivity, in its various forms, is antecedent to the development of drug addiction and an important behavioural trait underlying the inability of addicts to refrain from continued drug use. Impulsivity describes a variety of rapidly and prematurely expressed behaviours that span several domains from impaired response inhibition to an intolerance of delayed rewards, and is a core symptom of attention deficit hyperactivity disorder (ADHD) and other brain disorders. Various theories have been advanced to explain how impulsivity interacts with addiction both causally and as a consequence of chronic drug abuse; these acknowledge the strong overlaps in neural circuitry and mechanisms between impulsivity and addiction and the seemingly paradoxical treatment of ADHD with stimulant drugs with high abuse potential. Recent years have witnessed unprecedented progress in the elucidation of pharmacological mechanisms underpinning impulsivity. Collectively, this work has significantly improved the prospect for new therapies in ADHD as well as our understanding of the neural mechanisms underlying the shift from recreational drug use to addiction. In this review, we consider the extent to which pharmacological interventions that target impulsive behaviour are also effective in animal models of addiction. We highlight several promising examples of convergence based on empirical findings in rodent-based studies.

LINKED ARTICLES

This article is part of a themed section on Animal Models in Psychiatry Research. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-20

Abbreviations

5-CSRTT, five choice serial reaction time task; ADHD, attention deficit hyperactivity disorder; DD, delayed discounting; DRL, differential reinforcement of lower rates; FR, fixed ratio; HI, highly impulsive; ILC, infralimbic cortex; NAc, nucleus accumbens; NARI, noradrenaline re-uptake inhibitor; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PR, progressive ratio; SSRI, selective 5-HT re-uptake inhibitor; SSRTT, stop-signal reaction time task; STN, subthalamic nucleus; vHC, ventral hippocampus; VTA, ventral tegmental area

Table of Links

TARGETS	LIGANDS
α_1-adrenoceptor	Dopamine
α_2-adrenoceptor	5-HT
β_1-adrenoceptor	SB242084
β_2-adrenoceptor	WAY163909
D_1 receptor	Ketanserin
D_2 receptor	Desipramine
D_3 receptor	Yohimbine
5-HT_1 receptor	MK-801 (dizocilpine)
5-HT_2 receptor	GABA
5-HT_3 receptor	SR141716A (rimonabant)
5-HT_6 receptor	Neuropeptide Y
GluN2B receptor	Methamphetamine
$mGlu_1$ receptor	Cocaine
$mGlu_2$ receptor	Ethanol
$mGlu_5$ receptor	Atomoxetine
$mGlu_7$ receptor	Amphetamine
$GABA_A$ receptor	
$GABA_B$ receptor	
μ-opioid receptor	
δ-opioid receptor	
CB_1 receptor	
Nicotinic $\alpha4\beta2$ receptor	
M_1 receptor	
M_4 receptor	
NK_1 receptor	
Y_2 receptor	
H_3 receptor	
A_1 receptor	

This Table lists key protein targets and ligands in this document, which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (Alexander *et al.*, 2013a, Alexander *et al.*, 2013b).

Introduction

Drug addiction is a chronic, relapsing brain disorder for which surprisingly few effective therapies have been developed (O'Brien, 2008; Jupp and Lawrence, 2010; van den Brink, 2012; Pierce *et al.*, 2012). Although the precise brain mechanisms of addiction are unknown, this disorder is widely believed to engage individual biological risk factors that interact individually and collectively with drug-, stress- and other externally influenced brain plasticity mechanisms (Nestler, 2005; Uhl, 2006; Koob, 2008; Kalivas and Volkow, 2011). Consistent with this interpretation, personality traits such as novelty/sensation-seeking and impulsivity are widely recognized to predispose to addiction and modify disease progression (Chakroun *et al.*, 2004; Nigg *et al.*, 2006; Verdejo-Garcia *et al.*, 2008; Ersche *et al.*, 2010). Such traits share strong overlaps with structural and functional markers of addiction (Jupp and Dalley, 2014) and may, as a result, inform the neurobiological and pharmacological mechanisms of this disorder, thereby raising the possibility that modulating impulsivity may provide an approach through which risk for addiction and/or the addiction process may be remediated. Notably, in this regard, stimulant drugs such as d-amphetamine, which calm behaviour and reduce hyperactivity and impulsivity in attention deficit hyperactivity disorder (ADHD; Solanto, 1984; Fone and Nutt, 2005) are also prominent drugs of abuse. As a consequence, it has become an important open question whether treating ADHD with stimulant drugs accelerates, or conversely, offers protection against, the development of addiction (e.g. Barkley *et al.*, 2003). This paper reviews the evidence for convergent pharmacological mechanisms in impulsivity and addiction,

and additionally considers whether stimulant- and non-stimulant-based medications in ADHD may modify an individual's risk for addiction.

Defining impulsivity

Impulsivity describes an individual's tendency for premature, excessively risky, poorly conceived and inappropriate actions without due regard for future consequences (Daruma and Barnes, 1993). A range of behavioural processes are generally considered to contribute to this trait including urgency, risk-taking, sensation-seeking, behavioural disinhibition, impaired planning, lack of premeditation and insensitivity to punishment (Barratt, 1985; Evenden, 1999a; Monterosso and Ainslie, 1999; Moeller *et al.*, 2001; Whiteside and Lynam, 2003; Robbins *et al.*, 2012; Fineberg *et al.*, 2014). While impulsiveness is an important aspect of normal human behaviour, facilitating extraversion, sociability and appropriate risk-taking, the maladaptive expression of this trait has been associated with a number of neuropsychiatric morbidities including personality (Perry and Korner, 2011) and mood disorders (Lombardo *et al.*, 2012), suicide (Dougherty *et al.*, 2004), ADHD (Avila *et al.*, 2004), problem gambling (Verdejo-Garcia *et al.*, 2008) and drug addiction (Ersche *et al.*, 2010).

Impulsivity is a multifactorial trait often segregated according to motor disinhibition ('impulsive action') and impulsive decision making ('impulsive choice') (Winstanley *et al.*, 2006). In humans, it is generally assessed by self-report scales; for example, the Barratt Impulsivity Scale (BIS-11) (Barratt, 1985), the Urgency, Premeditation, Perseverance, Sensation-Seeking (UPSS) Impulsive Behaviour Scale (Whiteside and Lynam, 2003) and Dickman's Impulsivity Inventory (DII) (Dickman, 1990). Psychometric laboratory-based tasks can also be used to assess impulsivity; these overcome many of the limitations associated with self-report (e.g. see Wilson and Dunn, 2004) by providing more objective behavioural measures (Kertzman *et al.*, 2006; Chamberlain and Sahakian, 2007). In experimental animals, impulsive choice is frequently measured by operant-based delay-discounting tasks (Reynolds *et al.*, 2002; Cardinal, 2006). While several variants of this task are used, the general procedure involves a choice between a small immediate reward and a larger, but delayed reward. Impulsive choice is indexed by steeper reward discounting such that with increasing delay the perceived 'value' of reward diminishes and preference switches to small, immediate rewards. Action impulsivity can be assessed using a variety of operant paradigms; for example go/no-go visual and spatial discrimination tasks (Harrison *et al.*, 1999), which require inhibition of incorrect responses; the stop-signal reaction time task (SSRTT) where already initiated actions must be rapidly cancelled following presentation of an auditory or visual 'stop signal' stimulus (Eagle and Robbins, 2003). Impulsivity is assessed in these tasks by the number of inappropriate responses made. These include premature responses to a food-predictive cue on the five choice serial reaction time task (5-CSRTT) (Robbins, 2002), analogous to the differential responding for differential reinforcement of lower rate (DRL) task where responses made before a time interval has elapsed are punished (Evenden and Ryan, 1996; Evenden, 1999a).

Impulsivity and addiction

Impulsivity is widely regarded to contribute to the development of addiction, predicting initial drug use (Zernicke *et al.*, 2010), risk for addiction (Ersche *et al.*, 2010), rates of relapse (Muller *et al.*, 2008) and treatment retention (Moeller *et al.*, 2001). However, drugs of abuse can in turn affect levels of impulsivity (Jentsch and Taylor, 1999; Garavan *et al.*, 2008; de Wit, 2009) making it unclear whether co-expressed impulsivity in addicts (e.g. Petry, 2001; Moreno-Lopez *et al.*, 2012) is a cause or consequence of chronic drug use (Rogers and Robbins, 2001). In contrast, animal models of impulsivity help disambiguate causal relationships between impulsivity and addiction by enabling assessment prior to, and following, chronic drug exposure (Winstanley *et al.*, 2010a; Jupp *et al.*, 2013a). Collectively, these studies demonstrate that impulsivity affects different measures of addiction-related behaviour depending on drug class, baseline levels of impulsivity and specific impulsivity subtypes; they further demonstrate that drug use can, in turn, affect levels of impulsivity. For example, action impulsivity in rats precedes enhanced self-administration of a range of drugs, including stimulants (Dalley *et al.*, 2007; Belin *et al.*, 2008; Marusich and Bardo, 2009), alcohol (Radwanska and Kaczmarek, 2012) and nicotine (Diergaarde *et al.*, 2008), and predicts increased rates of relapse to cocaine-seeking (Economidou *et al.*, 2009). Similarly, choice impulsivity predicts increased alcohol (Poulos *et al.*, 1995; Oberlin and Grahame, 2009) and nicotine (Diergaarde *et al.*, 2008; Kayir *et al.*, 2014) consumption in rats, as well as resistance to extinction and enhanced relapse propensity to both nicotine (Diergaarde *et al.*, 2008) and cocaine (Broos *et al.*, 2012a). However, the relationship between choice impulsivity and drug reinforcement is not always clear (Broos *et al.*, 2012a; Schippers *et al.*, 2012), and this may reflect direct modulatory effects of cocaine and heroin on this particular measure of impulsivity (Mendez *et al.*, 2010; Schippers *et al.*, 2012).

Intriguingly, the effect of certain drugs on impulsivity often depends on baseline levels of impulsivity. For example, cocaine (Paine *et al.*, 2003; Roesch *et al.*, 2007; Winstanley *et al.*, 2009; Mendez *et al.*, 2010; Caprioli *et al.*, 2013) and nicotine (Kayir *et al.*, 2014) are reported to increase impulsivity in non-impulsive rats, but have the opposite effect in impulsive animals (Dalley *et al.*, 2007; Caprioli *et al.*, 2013; Kayir *et al.*, 2014; Kolokotroni *et al.*, 2014). It follows therefore that enhanced drug intake in impulsive animals may represent a form of 'self-medication' (Khantzian, 1985) analogous to the treatment of ADHD with stimulant drugs. Furthermore, the close interrelationship between impulsivity and addiction implies that they may share similar psychobiological mechanisms (e.g. an intolerance of delayed rewards) and that interventions that reduce impulsivity would have clinical benefits in addiction. In this review, we consider the strength of evidence implicating shared pharmacological mechanisms in impulsivity and rodent models of addiction-like behaviours and thus the feasibility of treating impulsivity to remediate addiction.

Animal models of addiction-like behaviour

While many rodent paradigms are available to model addiction-related processes, including reinforcement mechanisms (Sanchis-Segura and Spanagel, 2006), we have limited our discussion to studies involving drug self-administration and reinstatement procedures in rodents. These behavioural paradigms typically involve operant responding for i.v., or in the case of alcohol, oral drug reward, often in the presence of contingent and non-contingent cues and/or contexts, and typically either fixed ratio (FR – where a fixed number of responses result in reward) or progressive ratio (PR – where an incremental number of responses result in reward) reinforcement schedules. Relapse-like behaviour can be assessed in a number of ways, either following extinction of the learned association between contingent cues and contexts in the absence of drug availability, or after a period of forced abstinence. Relapse is triggered by exposing subjects to cues or contexts previously associated with drug availability (cue/context induced), a physical or chemical stressor (e.g. footshock, yohimbine) or following the administration of a priming dose of drug (i.e. drug-primed). It should be noted that these addiction-related behaviours only model aspects of the addiction construct and fail to recapitulate for example, the patterns of compulsive drug-seeking and intake associated with addiction. It has been suggested that the generally poor translation of preclinical and laboratory findings to positive clinical outcomes may be related to the limitations of these models to more fully encompass real world human addiction (Haney and Spealman, 2008). While such animal behavioural models have been developed (e.g. Deroche-Gamonet *et al.*, 2004; Vanderschuren and Everitt, 2004; Belin *et al.*, 2008) only a few studies to date have assessed the ability of specific pharmacological agents to disrupt these behaviours (Pelloux *et al.*, 2012). Importantly, in terms of the clinical applicability of the current review, the subtypes of impulsivity discussed have been demonstrated to predict vulnerability to addiction as assessed by these contemporary rodent models (e.g. Belin *et al.*, 2008).

Pharmacological mechanisms of impulsivity: convergent mechanisms with addiction

Dopaminergic agents

Dysfunction of the midbrain dopaminergic systems has been implicated in several forms of impulsive behaviour (Pattij and Vanderschuren, 2008; Dalley and Roiser, 2012) and widely in the development and persistence of addiction (Volkow *et al.*, 2004; Thomas *et al.*, 2008; Sulzer, 2011; George *et al.*, 2012) not least as all drugs of abuse exert effects on the mesocorticolimbic dopamine neurons (Di Chiara and Imperato, 1988). However, the modulation of impulsivity and addiction-related behaviours by dopamine is complex and in the case of impulsivity often variable depending on the precise measure of impulsivity (Tables 1 and 2).

In keeping with the efficacy of stimulant medications in ADHD, acute administration of cocaine, amphetamine and methylphenidate generally decreases impulsive choice in rats, increasing tolerance for delayed rewards in various discounting paradigms (Richards *et al.*, 1999; Wade *et al.*, 2000; Isles *et al.*, 2003; Winstanley *et al.*, 2003a; van Gaalen *et al.*, 2006a; Adriani *et al.*, 2007; Barbelivien *et al.*, 2008; Floresco *et al.*, 2008; Perry *et al.*, 2008; Krebs and Anderson, 2012). However, there have been notable exceptions (Evenden and Ryan, 1996; Cardinal *et al.*, 2000; Helms *et al.*, 2006; Stanis *et al.*, 2008a; Wooters and Bardo, 2011), which may reflect strain differences and paradigm-related effects. For example, methylphenidate reduces delay-discounting impulsivity in Wistar Kyoto rats, but has no effect in spontaneously hypertensive rats (Wooters and Bardo, 2011). Moreover, the presence of cues to signal delays can modulate the effects of stimulants in this task. Thus, amphetamine increases tolerance to cued delays (decreases impulsivity), but decreases tolerance to non-cued delays (Cardinal *et al.*, 2000). Stimulant medications also acutely increase impulsivity on tasks that assess action impulsivity; for example, the 5-CSRTT (Cole and Robbins, 1987; van Gaalen *et al.*, 2006b; Blondeau and Dellu-Hagedorn, 2007), but generally decrease impulsivity on the SSRTT (Feola *et al.*, 2000; Eagle and Robbins, 2003; Eagle *et al.*, 2007; 2009). These divergent effects lend support to the recently proposed dichotomy of 'waiting' versus 'stopping' forms of action impulsivity, which are differentially assayed by these two tasks (Dalley *et al.*, 2011).

Although stimulant drugs probably modulate impulsivity by enhancing dopaminergic tone, their effects are not always mirrored by drugs that act selectively through this mechanism, notably, dopamine re-uptake inhibitors (Table 1). Furthermore, the effect of amphetamine to reduce choice impulsivity is reduced in rats depleted of 5-HT (Winstanley *et al.*, 2003a). While these findings implicate additional neurotransmitters and mechanisms underlying the effects of indirect dopamine receptor agonists on impulsivity (including stimulants), the ability of directly acting D_1 and D_2-like receptor antagonists to oppose the effect of stimulants on impulsivity (e.g. van Gaalen *et al.*, 2006a,b) support a dopaminergic mechanism of action. Work over several years has localized these effects to specific corticostriatal sites (Table 2) with receptor subtype and region-specific effects. For example while oppositional effects of D_2-like receptor antagonism is observed between the nucleus accumbens (NAc) core and shell, decreasing and increasing impulsivity respectively in the 5-CSRTT (Besson *et al.*, 2010), a similar subregion-dependent distinction has not been reported for D_1 receptors (Pattij *et al.*, 2007a). It is unclear whether a similar divergence in dopaminergic modulation exists between the core and shell of the NAc with respect to impulsive choice; however, the effects of selective lesions of these subregions would appear to support this assertion (Ghods-Sharifi and Floresco, 2010). Further region-specific differentiation between D_1- and D_2-like receptor subtypes has been observed within the orbitofrontal cortex (OFC), with administration of a D_2/D_3, but not a D_1 receptor agonist found to reduce premature responding in highly impulsive (HI) animals (Winstanley *et al.*, 2010b). Similarly, administration of the D_2/D_3 receptor antagonist raclopride in the OFC increased impulsive choice, while a D_1 receptor antagonist had no effect (Pardey *et al.*, 2013). The significance of opponent interactions between NAc subregion and dopamine receptor subtype is unclear;

Table 1

Selected examples of the effects of acute systemic administration of dopaminergic compounds on measures of impulsivity and addiction-like behaviour in rodent models

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
Dopamine re-uptake inhibitor/releaser					
Amphetamine	↑ (Harrison *et al.*, 1997; van Gaalen *et al.*, 2006b)	↓ (Eagle *et al.*, 2009)	↑ (Evenden and Ryan, 1996; Cardinal *et al.*, 2000) ↓ (Wade *et al.*, 2000; van Gaalen *et al.*, 2006a)	↑ ethanol (Pfeffer and Samson, 1985) ↑ FR cocaine (Barrett *et al.*, 2004; Xi *et al.*, 2009) ↓ PR for cocaine (Xi *et al.*, 2009)	↑ cocaine (De Vries *et al.*, 1998a)
Cocaine	↑ (van Gaalen *et al.*, 2006b)				↑ cocaine (De Vries *et al.*, 1998a)
Methylphenidate	↑ (Navarra *et al.*, 2008b; Milstein *et al.*, 2010; Pattij *et al.*, 2012) =§ (Fernando *et al.*, 2012)	↓§ (Eagle *et al.*, 2007)	↓ (van Gaalen *et al.*, 2006a)	↑ FR cocaine (Hiranita *et al.*, 2011) ↑ FR nicotine (Wooters *et al.*, 2008)	↑ drug-primed cocaine (Schenk and Partridge, 1999; Broos *et al.*, 2012a) = cue-induced cocaine (Economidou *et al.*, 2011)
GBR12909	↑ (van Gaalen *et al.*, 2006b)	= (Bari *et al.*, 2009)	↓ (van Gaalen *et al.*, 2006a)	↓ FR cocaine (Tella, 1995; Schenk, 2002) ↑ FR cocaine (Barrett *et al.*, 2004)	↑ drug-primed cocaine (Schenk, 2002)
D_1 agonist					
SKF-81297	= (Winstanley *et al.*, 2010b)		= (Koffarnus *et al.*, 2011)	↓ FR ethanol (Cohen *et al.*, 1999) ↑ PR cocaine (Rowlett *et al.*, 2007)	↓ drug-primed cocaine (Self *et al.*, 1996)
SKF-82958				↓ FR cocaine (Caine *et al.*, 1999)	
D_1 antagonist					
SCH-23390	↓ (Harrison *et al.*, 1997; Koskinen and Sirvio, 2001; van Gaalen *et al.*, 2006a,b)	= (Bari and Robbins, 2013)	↑* (amphetamine) (van Gaalen *et al.*, 2006a), = (Wade *et al.*, 2000)	↓ PR cocaine (Hubner and Moreton, 1991; Depoortere *et al.*, 1993) ↑ FR cocaine (Koob *et al.*, 1987)	↓ drug-primed cocaine (Self *et al.*, 1996; Schenk and Gittings, 2003) ↓ context-induced cocaine (Broos *et al.*, 2012a) ↓ drug-primed MA (Carati and Schenk, 2011) ↓ cue-induced nicotine (Liu *et al.*, 2010)

Table 1

Continued

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
D_2 agonist					
Quinpirole	↓§ (Fernando *et al.*, 2012)		= (Koffarnus *et al.*, 2011)	↓ FR cocaine (Caine and Koob, 1993) ↓ FR ethanol (Cohen *et al.*, 1998) = PR MA (Izzo *et al.*, 2001)	↑ drug-primed cocaine (Self *et al.*, 1996), ↑ cocaine (De Vries *et al.*, 2002)
D_2 antagonist					
Eticlopride	= (van Gaalen *et al.*, 2006b) ↓* (amphetamine, cocaine, nicotine) (van Gaalen *et al.*, 2006b)		= (van Gaalen *et al.*, 2006a) ↑* (amphetamine) (van Gaalen *et al.*, 2006a)	↑ FR cocaine (Caine and Koob, 1994) ↓ PR cocaine (Ward *et al.*, 1996) ↓ PR MA (Izzo *et al.*, 2001)	↓ drug-primed cocaine (Schenk and Gittings, 2003) = drug-primed MA (Carati and Schenk, 2011) ↓ cue-induced nicotine (Liu *et al.*, 2010)
L741626	= (van Gaalen *et al.*, 2009) ↓* (amphetamine) (van Gaalen *et al.*, 2009)		= (Koffarnus *et al.*, 2011)		
Aripiprazole	↓§ (Besson *et al.*, 2010)			↑ FR cocaine (Roman *et al.*, 2013) ↓ PR MA (Wee *et al.*, 2007)	↓ cue-induced, drug-primed cocaine (Feltenstein *et al.*, 2007)
Sulpiride		= (Bari and Robbins, 2013)			
Haloperidol			= (Evenden and Ryan, 1996)		
Raclopride			↑ (Wade *et al.*, 2000)	↑ FR cocaine (Weissenborn *et al.*, 1996)	↓ drug-primed cocaine (Weissenborn *et al.*, 1996) ↓ context induced cocaine (Crombag *et al.*, 2002)
D_1/D_2 antagonist					
Flupenthixol	↓* (DOI) (Koskinen and Sirvio, 2001)		↑ (Cardinal *et al.*, 2000; Wade *et al.*, 2000)	↑ FR, ↓ PR cocaine (Richardson *et al.*, 1994)	
D_3 agonist					
7-OH-PIPAT		= (Bari and Robbins, 2013)		↓ FR, ↑ PR cocaine (Caine and Koob, 1995)	= drug-primed cocaine (Khroyan *et al.*, 2000)
D_3 antagonist					
Nafadotride	=§ (Besson *et al.*, 2010)	= (Bari and Robbins, 2013)			↓ cue-induced cocaine (Weiss *et al.*, 2001)

Table 1

Continued

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
SB277011	= (van Gaalen *et al.*, 2009) = * (amphetamine) (van Gaalen *et al.*, 2009)			↓ FR, PR cocaine (Song *et al.*, 2012) ↓ PR MA (Higley *et al.*, 2011) ↓ PR nicotine (Ross *et al.*, 2007) = FR nicotine (Kameda *et al.*, 2000) = FR ethanol (Heidbreder *et al.*, 2007)	↓ drug-primed MA (Higley *et al.*, 2011) ↓ drug-primed ethanol (Heidbreder *et al.*, 2007)
Pramipexole			= (Koffarnus *et al.*, 2011)		
PG01037			= (Koffarnus *et al.*, 2011)		
D_4 agonist					
PD168077		= (Bari and Robbins, 2013)			
D_4 antagonist					
L745870	↓* (methylphenidate) (Milstein *et al.*, 2010)	= (Bari and Robbins, 2013)	= (Koffarnus *et al.*, 2011)		
ABT724			↑ (Koffarnus *et al.*, 2011)		

*Denotes significant effect on pharmacologically increased (5-CSRTT)/decreased levels of impulsivity, agent in parentheses.
§Denotes effect in selected high-impulsive rats.
↑, increased; ↓, decreased; =, no effect; DD, delay discounting; DOI, (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride; MA, methamphetamine.

however, similar regional and neurochemical differentiation has been reported in the NAc of naturally occurring HI animals (Jupp *et al.*, 2013b; Simon *et al.*, 2013).

In keeping with an implicit role of enhanced dopaminergic neurotransmission in mediating drug reward and reinforcement, pharmacological agents affecting the dopaminergic systems have a range of effects on addiction-like behaviours in rodents. Systemic administration of D_1- and D_2-like receptor antagonists result in compensatory increases in responding for stimulant drugs under a FR schedule of reinforcement (e.g. Corrigall and Coen, 1991a; Barrett *et al.*, 2004), but decrease break points and thus motivation to work for drug under a PR schedule (e.g. Hubner and Moreton, 1991; Richardson *et al.*, 1994; Izzo *et al.*, 2001). By contrast, dopamine receptor agonists reduce responding for stimulant drugs under FR schedules, with D_2-like receptor agonists decreasing the rate of drug self-administration and D_1 receptor agonists increasing the latency to initiate this behaviour (Caine *et al.*, 1999); this distinction may reflect distinct roles of D_2 and D_1 receptors in drug reward and satiety (Suto and Wise, 2011). However, the effects of dopaminergic agents on opiate, alcohol and nicotine self-administration are less clear with conflicting effects of pharmacological blockade in some cases (e.g. Dyr *et al.*, 1993; David *et al.*, 2006; Rowlett *et al.*, 2007). Nevertheless, dopamine receptor antagonists, given either systemically or directly in the NAc generally inhibit reinstatement of drug-seeking for all major drug classes (reviewed in Self, 2010) . However, systemic D_1 receptor agonists fail to induce drug-seeking (Self *et al.*, 1996) and actually reduce both drug- and cue-induced relapse when given systemically (De Vries *et al.*, 1999). Thus, enhanced mesolimbic dopamine appears to trigger relapse through D_2 receptor mechanisms with D_2-like receptor agonists potentiating drug-seeking behaviour (Self *et al.*, 1996; Edwards *et al.*, 2007) Importantly, however, the effects of D_1 and D_2 receptor agonists, such as for impulsivity, appear again to be region-dependent, with D_1 receptor agonists in the NAc core and shell sufficient to stimulate drug relapse (Bachtell *et al.*, 2005), whereas D_2 receptor agonists increase relapse only when given in the NAc shell (Schmidt *et al.*, 2006). Similarly, while relapse/reinstatement can be blocked by the administration of D_1 receptor antagonists in the NAc shell (Bachtell *et al.*, 2005) and core

Table 2

Selected studies of region-specific dopaminergic interventions in impulsivity and addiction-related behaviour in rodent models

		Impulsive action		Impulsive choice		
Agent	**Region**	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
Dopamine re-uptake inhibitor/ releaser						
Amphetamine	NAc	↑ (Cole and Robbins, 1987)			↑ FR ethanol (Samson *et al.*, 1993; 1999)	
Methylphenidate	NAc core	↑ (Economidou *et al.*, 2012)				
	NAc shell	= (Economidou *et al.*, 2012)				
D_1 agonist						
SKF-38393	NAc	↑ (Pezze *et al.*, 2007)				
	NAc core					↑ cocaine (Bachtell *et al.*, 2005)
	NAc shell				= FR cocaine (Bachtell *et al.*, 2005)	↑ cocaine (Bachtell *et al.*, 2005)
	OFC	=§ (Winstanley *et al.*, 2010b)				
D_1 antagonist						
SCH-23390	NAc core	↓ (Pattij *et al.*, 2007a)	= (Eagle *et al.*, 2011)		↓ PR cocaine (Bari and Pierce, 2005)	↓ context-induced ethanol (Chaudhri *et al.*, 2009)
	NAc shell	↓ (Pattij *et al.*, 2007a)			↓ PR cocaine (Bari and Pierce, 2005) ↑ FR cocaine (Maldonado *et al.*, 1993)	↓ drug-primed cocaine (Bachtell *et al.*, 2005)
	DS	↓ (Agnoli and Carli, 2011)	↓ (Eagle *et al.*, 2011)		↑ FR cocaine (Caine and Koob, 1995; Caine *et al.*, 1995)	
	PFC			↑ (Loos *et al.*, 2010; Pardey *et al.*, 2013)	↓ PR cocaine (Olsen and Duvauchelle, 2006)	↓ stress-induced cocaine (Capriles *et al.*, 2003) = drug-primed cocaine (Capriles *et al.*, 2003) ↓drug-primed cocaine (Sun and Rebec, 2005)
	OFC	↓§ (Winstanley *et al.*, 2010b)		= (Pardey *et al.*, 2013)		↓ context-induced cocaine (Lasseter *et al.*, 2014) ↓ stress-induced cocaine (Capriles *et al.*, 2003)
	vHC			= (Abela and Chudasama, 2014)		

Table 2

Continued

		Impulsive action		Impulsive choice		
Agent	**Region**	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
D_2 agonist						
7-OH-DPAT	NAc				= FR cocaine (Bachtell *et al.*, 2005)	
Quinpirole		↑ (Pezze *et al.*, 2007)			↑ FR ethanol (Samson and Chappell, 2003)	↑ cocaine (shell) (Schmidt *et al.*, 2006)
	OFC	↓§ (Winstanley *et al.*, 2010b)				
D_2 antagonist						
Raclopride	OFC			↑ (Pardey *et al.*, 2013)		= stress, context-induced cocaine (Capriles *et al.*, 2003)
Sulpiride	DS		↑ (Eagle *et al.*, 2011)			
Eticlopride	NAc core	=* (amphetamine) (Pattij *et al.*, 2007a)			= FR cocaine (Bachtell *et al.*, 2005)	
Aripiprazole		=§ (Besson *et al.*, 2010)				
Sulpiride			= (Eagle *et al.*, 2011)			= drug-primed cocaine (Anderson *et al.*, 2006)
	NAc	= (Pezze *et al.*, 2007)			↑ FR ethanol (Levy *et al.*, 1991) ↑ FR cocaine, (Phillips *et al.*, 1994)	
	NAc shell					↓ drug-primed cocaine (Anderson *et al.*, 2006)
Aripiprazole		= § (Besson *et al.*, 2010)				
Eticlopride		=* (amphetamine) (Pattij *et al.*, 2007a)			↓ PR cocaine (Bari and Pierce, 2005) ↑ FR cocaine (Bachtell *et al.*, 2005)	↓ drug-primed cocaine (Bachtell *et al.*, 2005)
D_3 antagonist						
Nafadotride	NAc core	↓§ (Besson *et al.*, 2010)				
	NAc shell	↑§ (Besson *et al.*, 2010)				
SB-277011A	NAc					↓ stress-induced cocaine (Xi *et al.*, 2004)

*Denotes effect on pharmacologically increased/decreased levels of impulsivity, agent in parentheses.
§Denotes an effect in selected high-impulsive rats.
↑, increased; ↓, decreased; =, no effect; DS, dorsal striatum; MA, methamphetamine; vHC, ventral hippocampus.

(Chaudhri *et al.*, 2009) the effects of D_2 receptor antagonists are limited to the NAc shell (Anderson *et al.*, 2006).

The findings reviewed earlier, especially in relation to psychostimulants, are consistent with the effects of acute systemically administered dopaminergic agents on impulsive action (e.g. as measured in the 5-CSRTT), but not impulsive choice. Specifically, dopamine compounds that reduce or increase impulsive action also, in general, reduce or increase measures of drug reward and relapse (Table 1), with convergence in terms of both regional and dopamine receptor subtype specificity (Table 2). However, although systemically administered D_1 and D_2 receptor agonists enhance reward and at least in the case of D_2 receptors, stimulate relapse, dopamine receptor agonists either have no effect (D_1-like; Winstanley *et al.*, 2010b) or decrease premature responding in the 5-CSRTT (D_2-like; Besson *et al.*, 2010). Moreover, D_2-like receptor blockade in the NAc shell reduces drug reward and reinstatement (Anderson *et al.*, 2006), but increases premature responding in the 5-CSRTT (Besson *et al.*, 2010). Thus, manipulations that acutely alter dopamine receptor function appear unlikely to collectively suppress impulsivity and addiction-like behaviours.

5-Hydroxytryptaminergic agents

There is widespread support for a significant role of 5-HT in modulating impulsivity and addiction-related processes (Kranz *et al.*, 2010; Hayes and Greenshaw, 2011; Kirby *et al.*, 2011; Dalley and Roiser, 2012; Miyazaki *et al.*, 2012), through interactions with dopamine (Kapur and Remington, 1996; Di Matteo *et al.*, 2008) and other neurotransmitter systems (Fink and Gothert, 2007). A summary of the involvement of different 5-HT receptor subtypes in impulsivity and their putative loci of action is given in Tables 3 and 4. Near-complete depletion of 5-HT in the brain increases impulsivity in the 5-CSRTT (Harrison *et al.*, 1997; Winstanley *et al.*, 2004), the Go/No-go task (Harrison *et al.*, 1999) and the SSRTT (Eagle *et al.*, 2009). However, 5-HT depletion has variable effects on delay-discounting impulsivity, which may be due to differing experimental protocols (for discussion, see Winstanley *et al.* 2006). Similarly, enhancing 5-HT levels via systemically administered 5-HT re-uptake inhibitors reduces impulsivity in the 5-CSRTT (Baarendse and Vanderschuren, 2012; Humpston *et al.*, 2013), but has no effect on SSRTT performance (Bari *et al.*, 2009) or delay discounting (Evenden and Ryan, 1996; Baarendse and Vanderschuren, 2012). Studies of receptor selective ligands have predominantly implicated 5-HT_2 receptors in mediating these effects. 5-HT_{2C} receptor antagonists such as SB242084 increase premature responding in the 5-CSRTT (Winstanley *et al.*, 2004; Fletcher *et al.*, 2007) while the 5-HT_{2C} receptor agonist WAY163909 reduces impulsivity on this task (Navarra *et al.*, 2008a). Interestingly, the mixed 5-$HT_{2A/2C}$ receptor antagonist ketanserin reduced (Passetti *et al.*, 2003; Talpos *et al.*, 2006; Fletcher *et al.*, 2007), while the 5-$HT_{2A/2C}$ receptor agonist DOI ((+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride) increased premature responding in the 5-CSRTT (Koskinen *et al.*, 2000). Consistent with these results the selective 5-HT_{2A} receptor antagonist M100907 decreased premature responding (Winstanley *et al.*, 2003b; Fletcher *et al.*, 2007), similar to the effect of the mixed 5-$HT_{2B/C}$ receptor agonist Ro60-175 (Fletcher *et al.*, 2007). It is unclear whether delay discounting is also bi-directionally modulated by 5-HT_{2A} and 5-HT_{2C} receptors, but both ketanserin and the 5-HT_{2C} receptor antagonist SB242084 decrease this measure of impulsivity (Hadamitzky and Koch, 2009; Hadamitzky *et al.*, 2009; Paterson *et al.*, 2012). Finally, 5-HT_1 receptors have been implicated in several variants of impulsivity, but the results have been quite mixed. Thus, activation of 5-HT_{1A} receptors increases impulsivity on the delay-discounting task (Winstanley *et al.*, 2005b; van den Bergh *et al.*, 2006; Stanis *et al.*, 2008b; Blasio *et al.*, 2012) and either increases (Carli and Samanin, 2000), decreases (Blokland *et al.*, 2005) or has no effect (Winstanley *et al.*, 2003b; Carli *et al.*, 2006) on premature responding in the 5-CSRTT.

Wide-ranging evidence also implicates a role for 5-HT in reward and addiction (reviewed Filip *et al.*, 2010; Hayes and Greenshaw, 2011; Kirby *et al.*, 2011). However, owing to the complexity of this neurotransmitter system and its influence on dopamine and other neurotransmitter systems, the precise role of 5-HT in addiction-related processes is not always clear. Globally depleting 5-HT in the brain tends to potentiate drug reward, increasing stimulant drug self-administration under both FR and PR schedules (e.g. Lyness *et al.*, 1980; Roberts *et al.*, 1994) and drug-primed relapse (Tran-Nguyen *et al.*, 2001). Conversely, selective 5-HT re-uptake inhibitors generally decrease drug self-administration and relapse (Glatz *et al.*, 2002; Simon O'Brien *et al.*, 2011).

A survey of specific 5-HT receptor subtypes reveals that 5-HT_{1A} receptor activation enhances the rewarding effects of drugs by decreasing drug self-administration under FR schedules while increasing PR responding for cocaine (Peltier and Schenk, 1993; Parsons *et al.*, 1998) and alcohol (Wilson *et al.*, 1996) reinforcement. Tonic activity at 5-HT_{1A} receptors appears important for the rewarding effects of stimulant drugs, demonstrated by the inhibition of drug-primed reinstatement of cocaine-seeking by the selective 5-HT_{1A} receptor antagonist WAY100635 (Schenk, 2000; Burmeister *et al.*, 2004). Conversely, activation of 5-HT_{1B} receptors attenuates drug reward, increasing FR and decreasing PR responding for cocaine (Parsons *et al.*, 1998). Again, tonic activity at this receptor subtype appears important for cocaine-motivated behaviours, including reinstatement (David *et al.*, 2004; Przegalinski *et al.*, 2008).

However, the role of 5-HT_2 receptors in addiction-like behaviour is more nuanced. Thus, while systemically administered 5-HT_{2A} receptor antagonists appear to have no effect on the self-administration of cocaine or nicotine (Fletcher *et al.*, 2002; 2012; Nic Dhonnchadha *et al.*, 2009) they do reduce responding for alcohol when infused into the ventral tegmental area (Ding *et al.*, 2009). Selective 5-HT_{2A} receptor antagonists also inhibit drug- and cue-primed nicotine- and cocaine-seeking (Nic Dhonnchadha *et al.*, 2009; Fletcher *et al.*, 2012). The differential effect of these compounds on self-administration and relapse has been suggested to relate to the inhibition of dopamine release in the dorsal striatum, but not the NAc by these agents following drug administration (Murnane *et al.*, 2013). By contrast, selective 5-HT_{2C} receptor antagonists tend to increase rates of cocaine (Fletcher *et al.*, 2002) and alcohol (Tomkins *et al.*, 2002) self-administration, and drug-primed relapse (Burmeister *et al.*, 2004). Consistent with these findings, selective 5-HT_{2C} receptor agonists reduce self-administration and cue-induced cocaine (Cunningham *et al.*, 2011) and nicotine (Higgins *et al.*, 2012) reinstatement,

Table 3

Selected studies employing 5-hydroxytryptaminergic interventions in models of impulsivity and addiction-related behaviour in rodent models

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
5-HT re-uptake inhibitor/ releaser					
Citalopram	↓ (Baarendse and Vanderschuren, 2012; Humpston *et al.*, 2013)	= (Bari *et al.*, 2009)	= (Evenden and Ryan, 1996; Baarendse and Vanderschuren, 2012)	= FR cocaine (Hiranita *et al.*, 2009)	↓ drug-primed cocaine (Ruedi-Bettschen *et al.*, 2010)
Fluvoxamine	= (Tsutsui-Kimura *et al.*, 2009)			↓ FR ethanol (Lamb and Jarbe, 2001)	
Fluoxetine	↓ (Humpston *et al.*, 2013)			↓ FR ethanol (Simon O'Brien *et al.*, 2011) ↓ FR cocaine (Glatz *et al.*, 2002)	↓ stress- induced ethanol (Simon O'Brien *et al.*, 2011)
Paroxetine	↓ (Humpston *et al.*, 2013)				
5-HT depletion					
5,7-dihydroxytrypt-amine	↑ (Harrison *et al.*, 1997; Winstanley *et al.*, 2004)		↑ ((Wogar *et al.*, 1993; Bizot *et al.*, 1999; Mobini *et al.*, 2000) = (Winstanley *et al.*, 2003a; 2004)	↑ FR MA (Fletcher *et al.*, 1999) ↑ PR cocaine (Roberts *et al.*, 1994)	↓ cue-induced cocaine (Tran-Nguyen *et al.*, 2001) ↑ drug-primed cocaine (Tran-Nguyen *et al.*, 2001)
5-HT_{1A} agonist					
8-OH-DPAT	↑ (Carli and Samanin, 2000) = (Winstanley *et al.*, 2003b) ↓ (Blokland *et al.*, 2005)		↑ (Winstanley *et al.*, 2005b; Stanis *et al.*, 2008a; Blasio *et al.*, 2012)	↓ FR cocaine (Peltier and Schenk, 1993) ↓ PR cocaine (Parsons *et al.*, 1998) ↓ FR ethanol (Wilson *et al.*, 1996)	
Flesinoxan			↑ (van den Bergh *et al.*, 2006)		
5-HT_{1A} antagonist					
WAY100635	=/= * (methylphenidate) (Milstein *et al.*, 2010)				↓ drug-primed cocaine (Schenk, 2000; Burmeister *et al.*, 2004)
m-MPPI				↓ PR cocaine (Parsons *et al.*, 1998)	
5-HT_{1B} antagonist					
GR55562	=/= * (methylphenidate) (Milstein *et al.*, 2010)				
GR127935			= (van den Bergh *et al.*, 2006)		↓ drug-primed cocaine (Przegalinski *et al.*, 2008), ↓ cue-induced cocaine (Przegalinski *et al.*, 2008)

Table 3

Continued

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
5-$HT_{1A/1B}$ agonist					
Eltoprazine			↓ (van den Bergh *et al.*, 2006)		
RU24969	= (Evenden, 1999b)			↓ FR, ↑ PR cocaine (Parsons *et al.*, 1998)	↓ drug-primed cocaine (Acosta *et al.*, 2005) ↓ cue-induced cocaine (Acosta *et al.*, 2005)
5-HT_{2A} antagonist					
M100907	↓ (Winstanley *et al.*, 2003b; Fletcher *et al.*, 2007) ↓* (dizocilpine) (Higgins *et al.*, 2003) ↓* (5,7-dihydroxytryptamine) (Winstanley *et al.*, 2004)			= FR cocaine (Nic Dhonnchadha *et al.*, 2009) = PR cocaine (Fletcher *et al.*, 2002) = FR, PR nicotine (Fletcher *et al.*, 2012)	↓ cue-induced cocaine (Nic Dhonnchadha *et al.*, 2009) ↓ drug- primed nicotine, cue-induced nicotine (Fletcher *et al.*, 2012)
5-$HT_{2A/C}$ agonist					
DOI	↑ (Koskinen *et al.*, 2000; Blokland *et al.*, 2005)		↑ (Hadamitzky and Koch, 2009; Hadamitzky *et al.*, 2009; Blasio *et al.*, 2012)	↓ FR ethanol (Maurel *et al.*, 1999)	
5-$HT_{2A/C}$ antagonist					
Ketanserin	↓ (Passetti *et al.*, 2003; Talpos *et al.*, 2006; Fletcher *et al.*, 2007) ↓* (DOI) (Koskinen *et al.*, 2000)		↓* (DOI) (Hadamitzky and Koch, 2009; Hadamitzky *et al.*, 2009) = (Paterson *et al.*, 2012 22094071)	↓ FR nicotine (Levin *et al.*, 2008)	↓ cue-induced cocaine (Burmeister *et al.*, 2004)
Ritanserin	↓* (DOI) (Koskinen *et al.*, 2000)			= FR MA (Fletcher, 1998)	= cocaine (Schenk, 2000)
5-HT_{2C} agonist					
WAY163909	↓ (Navarra *et al.*, 2008a)			↓ FR cocaine (Cunningham *et al.*, 2011)	↓ cue-induced cocaine (Cunningham *et al.*, 2011)
Lorcaserin				↓ FR nicotine (Higgins *et al.*, 2012)	↓ nicotine, cue-induced nicotine (Higgins *et al.*, 2012)
5-HT_{2C} antagonist					
SB242084	↑ (Winstanley *et al.*, 2004; Fletcher *et al.*, 2007)		↓ (Paterson *et al.*, 2012)	↑ FR, PR cocaine (Fletcher *et al.*, 2002) ↑ FR ethanol (Tomkins *et al.*, 2002)	= cue-induced MA (Graves and Napier, 2012) ↑ drug-primed cocaine, (Burmeister *et al.*, 2004)

Table 3

Continued

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
5-$HT_{2B/C}$ agonist					
Ro60-0175	↓ (Fletcher *et al.*, 2007)			↓ FR, PR cocaine (Fletcher *et al.*, 2004) ↓ FR, PR nicotine (Fletcher *et al.*, 2012)	↓ cue-induced nicotine (Fletcher *et al.*, 2012) ↓ stress- induced cocaine (Fletcher *et al.*, 2008) ↓ context- induced cocaine (Fletcher *et al.*, 2008)
5-$HT_{2B/C}$ antagonist					
SER-082	= (Talpos *et al.*, 2006)		↓ (Talpos *et al.*, 2006)	= FR cocaine (Filip, 2005)	= cue-induced MA (Graves and Napier, 2012) = drug-primed cocaine (Filip, 2005) = cue-induced cocaine (Filip, 2005)
5-HT_{2B} antagonist					
SB215505	= (Fletcher *et al.*, 2007)			↓ FR, ↑PR cocaine (Fletcher *et al.*, 2002)	↑ cue-induced cocaine (Fletcher *et al.*, 2002)
5-HT_3 antagonist					
MDL72222	↓ (Evenden, 1999a)			↓ FR ethanol (McKinzie *et al.*, 2000) = FR nicotine (Corrigall and Coen, 1994) = PR cocaine (Lacosta and Roberts, 1993)	
Ondansetron				= FR cocaine (Lane *et al.*, 1992) ↓ PR cocaine (Davidson *et al.*, 2002)	↓ stress- induced ethanol (Le *et al.*, 2006)
5-HT_6 antagonist					
SB270146A	= (Talpos *et al.*, 2006)		= (Talpos *et al.*, 2006)		
CMP42	= (de Bruin *et al.*, 2013)			↓ FR nicotine (de Bruin *et al.*, 2013)	↓ cue- induced nicotine (de Bruin *et al.*, 2013) ↓ cue- induced ethanol (de Bruin *et al.*, 2013)

*Denotes effect on pharmacologically increased/decreased levels of impulsivity, agent in parentheses.
↑, increased; ↓, decreased; =, no effect; DOI, (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride; MA, methamphetamine.

an effect that appears to be mediated by the prefrontal cortex (PFC; Pentkowski *et al.*, 2010). Selective 5-HT_{2B} receptor antagonism enhances drug reward, reducing responding for cocaine under a FR schedule, while increasing responding under a PR schedule and augmenting drug-primed relapse behaviour (Fletcher *et al.*, 2002). However, mixed 5-$HT_{2B/C}$ receptor antagonists have no effect on drug self-administration or drug-seeking behaviour (Filip, 2005; Graves and Napier, 2012), although mixed 5-$HT_{2B/C}$ receptor agonists decreased these behaviours (Fletcher *et al.*, 2004; 2008; 2012). Finally, 5-HT_3 receptor antagonism generally reduces responding for ethanol and cocaine (Tomkins *et al.*, 1995;

Table 4

Selected studies of region-specific 5-hydroxytryptaminergic interventions in rodent models of impulsivity

Intervention	Region	Impulsive action 5-CSRTT	Impulsive choice DD
5-HT depletion			
5,7-dihydroxytryptamime	PFC	= (Fletcher *et al.*, 2009)	
	NAc	= (Fletcher *et al.*, 2009)	
5-HT_{1A} agonist			
8-OH-DPAT	PFC	= (Winstanley *et al.*, 2003b) =* (m-CPP) (Carli *et al.*, 2006)	
5-HT_{2A} antagonist			
M100907	PFC	↓ (Winstanley *et al.*, 2003b) = (Robinson *et al.*, 2008a) ↓* (m-CPP) (Carli *et al.*, 2006)	
	DS	↓* (m-CPP) (Agnoli and Carli, 2012)	
	NAc	↓ (Robinson *et al.*, 2008a)	
5-HT_{2C} antagonist			
SB242084	NAc	↑ (Robinson *et al.*, 2008a)	
	PFC	= (Robinson *et al.*, 2008a)	
5-$HT_{2A/C}$ agonist			
DOI	NAc Core	= (Koskinen and Sirvio, 2001)	
	NAc Shell	= (Koskinen and Sirvio, 2001)	
	OFC	= (Hadamitzky and Koch, 2009)	↑ (Wischhof *et al.*, 2011)
	BLA	= (Hadamitzky and Koch, 2009)	
	OFC + BLA	↑ (Hadamitzky and Koch, 2009)	
5-$HT_{2A/C}$ antagonist			
Ketanserin	PFC	↓ (Passetti *et al.*, 2003)	
	OFC	= (Hadamitzky and Koch, 2009)	
	BLA	= (Hadamitzky and Koch, 2009)	
	OFC + BLA	= (Hadamitzky and Koch, 2009)	
5-$HT_{2B/C}$ agonist			
Ro60-0175	DS	↓* (m-CPP) (Agnoli and Carli, 2012)	

*Denotes effect on pharmacologically increased/decreased levels of impulsivity, agent in parentheses.
↑, increased; ↓decreased; =, no effect; BLA, basolateral amygdala; m-CPP, meta-chloropiprazine; DOI, (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride; DS, dorsal striatum.

McKinzie *et al.*, 2000; Davidson *et al.*, 2002), similar to the effects of 5-HT_6 receptor antagonists, which decrease nicotine self-administration as well as both cue- and drug-primed relapse (de Bruin *et al.*, 2013).

The findings reviewed earlier indicate a significant overlap in 5-hydroxytryptaminergic mechanisms affecting impulsivity and addiction-like behaviours in rodents (Table 3). Again, similar to the effect at other transmitter systems, pharmacological agents that reduce impulsive action (rather than impulsive choice) also reduce drug self-administration and drug-seeking, whereas agents that enhance impulsive action also potentiate addiction-like behaviours. However, despite an involvement of 5-HT_{1A}, 5-HT_{1B} and 5-HT_6 receptors in reward and addiction-like behaviour (reviewed earlier), there is no convincing evidence they play a major role in impulsive action.

Noradrenergic agents

A role for noradrenaline in impulsivity is substantiated by the clinical efficacy of amphetamine and methylphenidate in ADHD, which act to enhance noradrenaline as well as dopamine transmission in the brain [reviewed in Del Campo *et al.* (2011)] and more specifically by the effectiveness of the selective noradrenaline re-uptake inhibitor (NARI) atomoxetine in ADHD (Simpson and Plosker, 2004; Faraone *et al.*, 2005) and animal models of impulsivity (Blondeau and Dellu-Hagedorn, 2007; Navarra *et al.*, 2008b; Robinson *et al.*, 2008b; Tsutsui-Kimura *et al.*, 2009; Fernando *et al.*, 2012; see Table 5). In addition, mixed 5-HT/noradrenaline re-uptake inhibitors such as desipramine (van Gaalen *et al.*, 2006b; Paine *et al.*, 2007), milnacipran (Tsutsui-Kimura *et al.*, 2009) and venlafaxine (Humpston *et al.*, 2013) are effective in

Table 5

Selected studies of systemically administered (unless otherwise stated) noradrenergic interventions in rodent models of impulsivity and addiction-like behaviour

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
NA re-uptake inhibitor					
Atomoxetine	↓§ (Blondeau and Dellu-Hagedorn, 2007; Fernando *et al.*, 2012) ↓ (Navarra *et al.*, 2008b; Robinson *et al.*, 2008b; Tsutsui-Kimura *et al.*, 2009)	↓ (Robinson *et al.*, 2008b; Bari *et al.*, 2009)	↓ (Robinson *et al.*, 2008b) = (Baarendse and Vanderschuren, 2012) ↑ (Broos *et al.*, 2012b)		↓ cue-induced cocaine (Economidou *et al.*, 2009; 2011)
Reboxetine	↓ (Liu *et al.*, 2009)			↓ FR nicotine (Rauhut *et al.*, 2002)	
NA/DA re-uptake inhibitor					
Buproprion	= (Humpston *et al.*, 2013)			↓ FR MA (Reichel *et al.*, 2009) ↓ FR nicotine (Liu *et al.*, 2008) = PR nicotine (Bruijnzeel and Markou, 2003)	↑ cue-induced nicotine (Liu *et al.*, 2008)
NA/5-HT re-uptake inhibitor					
Desipramine	↓ (van Gaalen *et al.*, 2006b; Paine *et al.*, 2007; Pattij *et al.*, 2012)		= (van Gaalen *et al.*, 2006a)	= FR cocaine (Tella, 1995)	↓ cue-induced ethanol (Simon O'Brien *et al.*, 2011)
Milnacipran	↓ (Tsutsui-Kimura *et al.*, 2009)				↓ cue-induced ethanol (Simon O'Brien *et al.*, 2011)
Subutramine	= (Humpston *et al.*, 2013)				
Venlafaxine	↓ (Humpston *et al.*, 2013)				
α_1 agonist					
Phenylephrine			= (van Gaalen *et al.*, 2006a)		
α_1 antagonist					
Prazosin	↓ (Liu *et al.*, 2009) ↓* (DOI) (Koskinen *et al.*, 2003)			= FR cocaine (Ecke *et al.*, 2012) ↓ FR nicotine (Forget *et al.*, 2010)	↓ stress- induced ethanol (Le *et al.*, 2011) ↓ drug- primed cocaine (Zhang and Kosten, 2005) ↓ drug-primed, cue-induced nicotine (Forget *et al.*, 2010)

Table 5

Continued

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT**	**DD**	**Self-administration**	**Reinstatement**
α_2 agonist					
Guanfacine	↓§ (Fernando *et al.*, 2012) ↓ (Milstein *et al.*, 2007)		↓ vHC (Abela and Chudasama, 2014)		↓ stress-induced cocaine (Buffalari *et al.*, 2012) ↓ stress- induced ethanol (Le *et al.*, 2011) ↓ cue-induced cocaine (Smith and Aston-Jones, 2011)
Clonidine			↑ (van Gaalen *et al.*, 2006a)		↓ stress- induced cocaine (Erb *et al.*, 2000) = drug primed cocaine (Erb *et al.*, 2000) ↓ stress- induced nicotine (Zislis *et al.*, 2007)
Lofexidine				↓ FR ethanol (Le *et al.*, 2005)	↓ stress- induced ethanol (Le *et al.*, 2005)
Imidazoline					↓ cue- induced cocaine (Smith and Aston-Jones, 2011)
α_2 antagonist					
Yohimbine	↑ (Sun *et al.*, 2010; Torregrossa *et al.*, 2012)			↑ FR ethanol (Le *et al.*, 2005) ↑FR, PR nicotine (Li *et al.*, 2012)	↑ cocaine (Feltenstein and See, 2006) ↑ MA (Shepard *et al.*, 2004) ↑ ethanol (Le *et al.*, 2005) ↑ nicotine (Feltenstein *et al.*, 2012) ↑ cue- induced cocaine (Feltenstein *et al.*, 2011; Buffalari *et al.*, 2012)
Atipamezole	↑ (Koskinen *et al.*, 2003)				
Idazoxan	= (Humpston *et al.*, 2013)				
β_2 agonist					
Clenbuterol	↓ (Pattij *et al.*, 2012)				
β antagonist					
Propranolol	↓* (methylphenidate) (Milstein *et al.*, 2010)			↓ FR, PR ethanol (Gilpin and Koob, 2010) ↓ FR cocaine (Harris *et al.*, 1996)	↓ cue- induced nicotine (Chiamulera *et al.*, 2010)

*Denotes effect on pharmacologically increased/decreased levels of impulsivity, agent in parentheses.
§Denotes an effect in selected high-impulsive rats.
↑, increased; ↓ decreased; = no effect; MA, methamphetamine; vHC, ventral hippocampus.

reducing action impulsivity. These findings contrast with the mixed dopamine/noradrenaline re-uptake inhibitor buproprion, which has no effect on impulsive action (Humpston *et al.*, 2013) presumably as a result of opponent effects of dopamine on this task (Dalley *et al.*, 2011). The effects of noradrenaline on impulsive action appear to be mediated by α_{1}-, α_{2}- and β_2-adrenoceptors. Thus, systemic administration of α_1 receptor antagonists (Milstein *et al.*, 2007; Liu *et al.*, 2009) and α_2-adrenoceptor agonists (Milstein *et al.*, 2007; Fernando *et al.*, 2012) reduce, whereas α_2-adrenoceptor antagonists, increase action impulsivity (Koskinen *et al.*, 2003; Sun *et al.*, 2010; Torregrossa *et al.*, 2012). An action at β-adrenoceptors has also been implicated in this form of impulsivity, with a recent study demonstrating an effect of the β_2-adrenoceptor selective agonist clenbuterol to reduce impulsivity, as measured by the 5-CSRTT (Pattij *et al.*, 2012). This appears somewhat at odds with data demonstrating an effect of the non-selective β-adrenoceptor antagonist propranolol to reduce premature responding induced by methylphenidate (Milstein *et al.*, 2010). Clearly further studies are required to delineate the relative contributions of β_1- and β_2-adrenoceptors to this behaviour.

While there is conflicting evidence for a role of NARIs in impulsive choice (van Gaalen *et al.*, 2006a; Robinson *et al.*, 2008b; Baarendse and Vanderschuren, 2012; Broos *et al.*, 2012b), systemic administration of the α_2-adrenoceptor agonist clonidine appears to increase this form of impulsivity (van Gaalen *et al.*, 2006a), but curiously has the opposite effect when infused directly in the hippocampus (Abela and Chudasama, 2014). Consistent with region-specific effects of noradrenaline transmission on distinct impulsivity subtypes a recent study found that atomoxetine reduces impulsivity in the 5-CSRTT when administered in the NAc shell, but not the NAc core or the PFC (Economidou *et al.*, 2012).

Noradrenaline is thought to contribute to drug reward and addiction through dopamine-dependent and dopamine-independent processes (reviewed in Weinshenker and Schroeder, 2007). Pharmacological manipulation of this system affects several measures of addiction-related behaviours in rodents (Table 5). While these generally have little effect on psychostimulant self-administration (reviewed in Sofuoglu and Sewell, 2009) there is mounting evidence that noradrenergic mechanisms modulate ethanol, nicotine and opiate self-administration, specifically *via* α_1- (Rasmussen *et al.*, 2009; Forget *et al.*, 2010), but not α_2- (Le *et al.*, 2005; Marinelli *et al.*, 2007; Li *et al.*, 2014) adrenoceptors. Thus, α_1-adrenoceptor antagonists such as prazosin attenuate drug-primed reinstatement (Zhang and Kosten, 2005), putatively by decreasing dopamine release in the NAc (Lane *et al.*, 1988).

Previous research indicates that noradrenaline plays a critical role in cue- and stress-induced drug relapse. Atomoxetine has been found to inhibit cue-induced cocaine reinstatement (Economidou *et al.*, 2009; 2011), while the mixed 5-HT/noradrenaline re-uptake inhibitors desipramine and milnacipran reduce cue-induced ethanol reinstatement (Simon O'Brien *et al.*, 2011). Conversely, the mixed noradrenaline/dopamine re-uptake inhibitor buproprion *enhances* nicotine cue-induced reinstatement (Liu *et al.*, 2008) presumably as a consequence of increased tonic activity at dopamine receptors. In terms of specific receptor subtypes α_1-adrenoceptor antagonists (e.g. Forget *et al.*, 2010; Le *et al.*, 2011) and α_2-adrenceptor agonists (e.g. Erb *et al.*, 2000; Le *et al.*, 2005; Zislis *et al.*, 2007; Smith and Aston-Jones, 2011) reduce reinstatement to drug-associated cues and various stressors. By contrast, the α_2-adrenoceptor antagonist yohimbine facilitates reinstatement to all major classes of abused drugs (psychostimulants, alcohol, opiates, nicotine) (Shepard *et al.*, 2004; Le *et al.*, 2005; Feltenstein and See, 2006; Banna *et al.*, 2010; Feltenstein *et al.*, 2012). Yohimbine also potentiates the effects of cue-exposure on cocaine-seeking (Feltenstein *et al.*, 2011). In addition, β-adrenoceptors contribute to cue- and stress-induced reinstatement (e.g. Leri *et al.*, 2002; Chiamulera *et al.*, 2010).

In keeping with the findings reviewed to date, there is considerable overlap in noradrenergic manipulations of impulsive action and addiction-like behaviour. Thus, drugs that decrease action impulsivity also act to reduce drug self-administration and/or inhibit relapse and *vice versa*. However, there is little overlap of these behaviours with impulsive choice (Table 5).

Glutamatergic agents

As shown in Table 6, systemic administration of non-competitive glutamatergic NMDA receptor antagonists predominantly have the effect of increasing impulsive action (Amitai *et al.*, 2007; Paine *et al.*, 2007; Oliver *et al.*, 2009; Fletcher *et al.*, 2011) and impulsive choice (Floresco *et al.*, 2008; Cottone *et al.*, 2013). At least in the case of impulsive action this effect appears to be mediated by GluN2B-containing receptors (for nomenclature see Alexander *et al.*, 2013b). Thus, the selective GluN2B NMDA receptor antagonist Ro63-1908 decreased impulsivity in the 5-CSRTT (Higgins *et al.*, 2005; Burton and Fletcher, 2012). Qualitatively similar effects are reported for metabotropic glutamate receptor (mGlu) antagonists (for nomenclature see Alexander *et al.*, 2013a), specifically acting at the $mGlu_5$ subtype on the 5-CSRTT (Semenova and Markou, 2007). Interestingly, $mGlu_1$ receptor antagonism decreased impulsive choice on a delay-discounting task (Sukhotina *et al.*, 2008).

While there is an abundance of evidence implicating NMDA, AMPA, kainic acid receptors, metabotropic receptors [e.g. $mGlu_7$ (Li *et al.*, 2010)] and excitatory amino acid transporters in addiction-related behaviours (for a comprehensive review, see Gass and Olive, 2008), we have limited our discussion to only those glutamatergic agents evaluated in rodent models of impulsivity. NMDA receptor antagonists generally attenuate drug self-administration and measures of drug reward including conditioned-place preference (e.g. Hyytia *et al.*, 1999; Glick *et al.*, 2001; Blokhina *et al.*, 2005; Yonghui *et al.*, 2006; Sabino *et al.*, 2013). One notable exception, however, is MK-801, which increases cocaine self-administration (Allen *et al.*, 2005) and augments relapse to cocaine (De Vries *et al.*, 1998b). Curiously, MK-801 also inhibits cue-induced relapse to ethanol (von der Goltz *et al.*, 2009), an effect resembling the actions of selective GluN2B NMDA receptor antagonists to reduce drug- and cue-induced reinstatement of ethanol (Vengeliene *et al.*, 2005; Wang *et al.*, 2010) and nicotine seeking (Gipson *et al.*, 2013). Systemically administered GluN2B receptor antagonists also reduce the self-administration of ethanol in rats (Wang *et al.*, 2010). Other studies have shown that $mGlu_1$, $mGlu_{2/3}$ and $mGlu_5$ receptor antagonists reduce self-administration of, and

Table 6

Selected studies of systemically administered (unless otherwise stated) interventions of glutamatergic, GABAergic, opioidergic, cholinergic and cannabinoid neurotransmission in rodent models of impulsivity and addiction-like behaviour

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT/Go/No-go**	**DD**	**Self-administration**	**Reinstatement**
Glutamate					
Non-competitive NMDA antagonist					
MK-801	↑ (Paine *et al.*, 2007)			↓FR, ↑PR cocaine (Allen *et al.*, 2005)	↓ cue-induced ethanol (von der Goltz *et al.*, 2009)
Ketamine	↑ (Oliver *et al.*, 2009) = (Nemeth *et al.*, 2010)		↑ (Cottone *et al.*, 2013) ↑ (Floresco *et al.*, 2008)	↓ FR ethanol (Sabino *et al.*, 2013)	
Memantine			↑ (Cottone *et al.*, 2013) = (Oberlin *et al.*, 2010)	↓ FR ethanol (Sabino *et al.*, 2013) ↓FR, PR cocaine (Hyytia *et al.*, 1999)	
PCP	↑ (Amitai *et al.*, 2007)			↓FR ethanol (Shelton and Balster, 1997)	
Selective glutamate receptor antagonist					
Ro63-1908 (NMDA 2B)	↑ (Higgins *et al.*, 2005; Burton and Fletcher, 2012)				
Ifenprodil (NMDA 2B)					↓ drug-primed ethanol (Vengeliene *et al.*, 2005) ↓ cue-induced nicotine (Gipson *et al.*, 2013)
EMQMCM ($mGlu_1$)			↓ (Sukhotina *et al.*, 2008)		↓ cue-induced nicotine, drug-primed nicotine (Dravolina *et al.*, 2007)
JNJ16259685 ($mGlu_1$)					↓ context- induced cocaine (Xie *et al.*, 2012b)
LY341495 ($mGlu_{2/3}$)	= (Semenova and Markou, 2007)			↓FR, ↓PR cocaine (Allen *et al.*, 2005) ↓ FR ethanol (Backstrom and Hyytia, 2005)	↓ cue-induced ethanol (Backstrom and Hyytia, 2005) ↓ cue-induced cocaine (Baptista *et al.*, 2004)

Table 6

Continued

Agent	Impulsive action: 5-CSRTT	Impulsive action: SSRTT/Go/No-go	Impulsive choice: DD	Self-administration	Reinstatement
MPEP ($mGlu_5$)	↓ (Semenova and Markou, 2007)			↓ FR ethanol (Schroeder *et al.*, 2005) ↓FR, ↓PR nicotine (Paterson and Markou, 2005) ↓FR, PR cocaine (Paterson and Markou, 2005)	↓ cue-induced cocaine (Backstrom and Hyytia, 2006) ↓cue-induced nicotine (Palmatier *et al.*, 2008) ↓ drug-primed nicotine (Tessari *et al.*, 2004)
GABA					
GABA-mimetic					
Ethanol	↑ (Oliver *et al.*, 2009)		↑ (Olmstead *et al.*, 2006)	↓ FR ethanol (Shelton and Balster, 1997)	
Vigabatrin				↓ FR cocaine (Filip *et al.*, 2007)	↓ drug-primed cocaine (Filip *et al.*, 2007)
$GABA_A$ agonist					
Diazepam	↑ (Oliver *et al.*, 2009) = § (Molander *et al.*, 2011)		↑ (Thiebot *et al.*, 1985)	↓ FR cocaine (Augier *et al.*, 2012)	
Chlordiazepoxide			↑ (Cardinal *et al.*, 2000)		
$GABA_B$ agonist					
Baclofen	↑ ILC (Murphy *et al.*, 2012) ↑ MRN (Le *et al.*, 2008) ↓ STN (Baunez and Robbins, 1999)		↑ OFC (Zeeb *et al.*, 2010) ↑ vHC (Abela and Chudasama, 2014) ↑ NAc Core (Ghods-Sharifi and Floresco, 2010) = NAc Shell (Ghods-Sharifi and Floresco, 2010) ↓ STN (Winstanley *et al.*, 2005a)	↓ FR, PR cocaine (Brebner *et al.*, 2000) ↓ FR nicotine (Fattore *et al.*, 2002)	↓ drug-primed nicotine (Fattore *et al.*, 2009)
Opioid					
Non-selective antagonist					
Naloxone	= (Pattij *et al.*, 2009; Wiskerke *et al.*, 2011b) = * (nicotine) (Wiskerke *et al.*, 2012) ↓* (amphetamine, GBR12909) (Wiskerke *et al.*, 2011b)	= (Pattij *et al.*, 2009)	= (Pattij *et al.*, 2009) =/= * (amphetamine) (Wiskerke *et al.*, 2011b)	↓ FR cocaine (Kiyatkin and Brown, 2003) ↓ FR nicotine (Ismayilova and Shoaib, 2010)	↓ drug-primed cannabinoid (Spano *et al.*, 2004)

Table 6

Continued

Agent	Impulsive action		Impulsive choice		
	5-CSRTT	SSRTT/Go/No-go	DD	Self-administration	Reinstatement
μ agonist					
Morphine	↑ (Pattij *et al.*, 2009)	= (Pattij *et al.*, 2009)	↑ (Pattij *et al.*, 2009)		
δ antagonist					
Naltrindol	=/= * (amphetamine) (Wiskerke *et al.*, 2011b)		=/= * (amphetamine) (Wiskerke *et al.*, 2011b)	= FR nicotine (Ismayilova and Shoaib, 2010) = FR cocaine (de Vries *et al.*, 1995)	↓ cue-induced ethanol (Ciccocioppo *et al.*, 2002; Marinelli *et al.*, 2009)
κ agonist					
Salvinorin A	= (Nemeth *et al.*, 2010)				
U50 488		↑ (Walker and Kissler, 2013)	= (Walker and Kissler, 2013)	↓FR nicotine (Ismayilova and Shoaib, 2010) ↓FR cocaine (Glick *et al.*, 1995)	
U69593					↓ drug-primed cocaine (Schenk *et al.*, 2000)
κ antagonist					
Nor-BNI	=/= * (amphetamine, nicotine) (Wiskerke *et al.*, 2011b; 2012)	= (Walker and Kissler, 2013)	=/= * (amphetamine) (Wiskerke *et al.*, 2011b)	= FR cocaine (Glick *et al.*, 1995) ↓ PR cocaine (Wee *et al.*, 2009) ↓ FR ethanol (Walker *et al.*, 2011)	↓ stress- induced cocaine (Redila and Chavkin, 2008)
Cannabinoid					
CB_1 agonist					
WIN 55212-2	= (Pattij *et al.*, 2007b)		= (Pattij *et al.*, 2007b)	↑ FR nicotine (Gamaleddin *et al.*, 2012)	↑ drug-primed, cue- induced nicotine (Gamaleddin *et al.*, 2012) ↑ drug-primed ethanol (Alen *et al.*, 2008)
CB_1 antagonist					
SR141716A	=/= * (GBR12909)/↓* (nicotine) (Wiskerke *et al.*, 2012) ↓* (amphetamine) (Wiskerke *et al.*, 2011a) ↓ (Pattij *et al.*, 2007b)		= (Pattij *et al.*, 2007b) ↑* (amphetamine) (Wiskerke *et al.*, 2011a)	↓FR, PR ethanol (Economidou *et al.*, 2006) = FR cocaine (De Vries *et al.*, 2001)	↓ cue-induced ethanol (Economidou *et al.*, 2006) ↓ cue-induced cocaine (De Vries *et al.*, 2001)

Table 6

Continued

	Impulsive action		Impulsive choice		
Agent	**5-CSRTT**	**SSRTT/Go/No-go**	**DD**	**Self-administration**	**Reinstatement**
SLV330	↓ (de Bruin *et al.*, 2011)			↓FR ethanol, nicotine (de Bruin *et al.*, 2011)	↓ cue-induced ethanol, nicotine (de Bruin *et al.*, 2011)
O-2050	↓/↓* (amphetamine) (Wiskerke *et al.*, 2011a)		↑* (amphetamine) (Wiskerke *et al.*, 2011a)		
Cholinergic					
nACh agonist					
Nicotine	↑ (Blondel *et al.*, 2000)	↑ (Kolokotroni *et al.*, 2011)	↑ (Dallery and Locey, 2005; Kolokotroni *et al.*, 2011)		
nACh antagonist					
Mecamylamine (α4β2)	↓ (Ruotsalainen *et al.*, 2000; Tsutsui-Kimura *et al.*, 2010) ↓* (nicotine) (Kolokotroni *et al.*, 2011)		= (Mendez *et al.*, 2012) ↓* (nicotine) (Kolokotroni *et al.*, 2011)	↓ FR cocaine (Levin *et al.*, 2000) ↓ FR ethanol (Kuzmin *et al.*, 2009) ↓ FR nicotine (Watkins *et al.*, 1999)	↓ cue-induced nicotine (Liu *et al.*, 2007)
Methyllycaconitine (α7)	= (Tsutsui-Kimura *et al.*, 2010)			= FR ethanol (Le *et al.*, 2000)	= cue-induced nicotine (Liu, 2014) = drug-primed ethanol (Kuzmin *et al.*, 2009)
Non-selective mACh agonist					
Oxotremorine	= (Mirza and Stolerman, 2000)		= (Mendez *et al.*, 2012)	↓ FR cocaine (Rasmussen *et al.*, 2000; Thomsen *et al.*, 2010)	
Non-selective mACh antagonist					
Scopolamine	= (Ruotsalainen *et al.*, 2000) ↑ (Shannon and Eberle, 2006) ↓ (Mirza and Stolerman, 2000)		↑ (Mendez *et al.*, 2012)	↓ ethanol (Rezvani *et al.*, 1991)	↓ drug-primed cocaine (Yee *et al.*, 2011)
Atropine			↑ (Mendez *et al.*, 2012)	↓ FR amphetamine (Davis and Smith, 1975)	

*Denotes effect on pharmacologically increased levels of impulsivity, agent in parentheses.
§Denotes effect in selected high-impulsive rats.
↑, increased; ↓, decreased; =, no effect; BLA, basolateral amygdala; ILC, infralimbic cortex; MA, methamphetamine; mACh, muscarinic ACh receptor; MRN, median raphe nucleus; nACh, nicotinic ACh receptor; PCP, phencyclidine; STN, subthalamic nucleus; vHC, ventral hippocampus.

relapse to, many classes of abused drugs (e.g. Backstrom and Hyytia, 2005; Dravolina *et al.*, 2007; Xie *et al.*, 2010; 2012b).

In view of the predominantly consistent effect of antagonism at NMDA and mGlu receptors to enhance measures of action impulsivity, but *reduce* self-administration and relapse-like behaviour, it is unlikely that the link between action impulsivity and addiction is driven via activity in the glutamatergic system. There is the possibility, however, that action at $mGlu_1$ receptors may link addiction-related behaviours and impulsive choice given that antagonism at this receptor subtype commonly reduces both behavioural categories (e.g. Dravolina *et al.*, 2007; Sukhotina *et al.*, 2008).

GABAergic agents

While few studies have investigated the role of GABA in impulsivity (Hayes *et al.*, 2014), $GABA_A$ and $GABA_B$ agonists have generally been found to increase measures of impulsive action (Oliver *et al.*, 2009) and impulsive choice (Thiebot *et al.*, 1985; Cardinal *et al.*, 2000; Olmstead *et al.*, 2006; Table 6). However, enhancing GABAergic activity tends to decrease drug self-administration (Augier *et al.*, 2012) and relapse to drug-seeking (Filip *et al.*, 2007; Fattore *et al.*, 2009). Nevertheless, intracerebral infusions of GABA agonists have been shown to reduce impulsivity (e.g. Baunez and Robbins, 1999) suggesting that activity in local GABAergic microcircuits may bear a closer correspondence with impulsivity and addiction-related behaviours.

Opioidergic agents

Systemic administration of the non-selective μ-opioid receptor agonist morphine has been found to increase impulsivity in both delay discounting and the 5-CSRTT (Pattij *et al.*, 2009). At least for impulsive action, phasic activation at δ-opioid receptors has also been implicated in enhancing impulsivity (Befort *et al.*, 2011). Interestingly, antagonism at μ-opioid receptors has been shown to attenuate the effects of amphetamine and the dopamine re-uptake inhibitor GBR12909 to increase impulsivity in this task (Wiskerke *et al.*, 2011b), suggesting again that dopamine transmission is subject to modulation by a myriad of neurotransmitters, putatively at the level of the mesolimbic dopamine system (Diergaarde *et al.*, 2008). There is little evidence, however, for tonic activity at opioid receptors in mediating impulsive action or choice (e.g. Pattij *et al.*, 2009; Wiskerke *et al.*, 2011b; 2012).

Available evidence suggests some overlap between opioidergic mechanisms capable of affecting both impulsivity and addiction-related behaviours (Table 6). In general, μ- and δ-opioid receptor agonists are capable of enhancing drug self-administration (e.g. Sabino *et al.*, 2007) and relapse-like behaviour (e.g. Simmons and Self, 2009), although it should be noted that there was regional specificity in these effects (reviewed in Le Merrer *et al.*, 2009). Unlike the null findings for impulsivity, however, μ- and δ-opioid receptor antagonists generally reduce these behaviours [(e.g. Corrigall and Coen, 1991b; Ciccocioppo *et al.*, 2002; Kiyatkin and Brown, 2003; Spano *et al.*, 2004); for review, see van Ree *et al.*, 1999]. It remains to be seen whether such antagonists are capable of reducing impulsivity in animals with endogenously enhanced levels of this trait.

Cannabinoids

Despite a relative paucity of studies, the cannabinoid system offers potential scope for pharmacological intervention in both impulsivity and addiction. For example, tonic activity at cannabinoid type 1 receptors has been found to modulate nicotine-induced increases in impulsive responding on the 5-CSRTT (Wiskerke *et al.*, 2012). Furthermore, selective CB_1 receptor antagonists are capable of reducing baseline impulsivity as measured on this task (Pattij *et al.*, 2007b; de Bruin *et al.*, 2011); however, they have been found to have no effect on delay-discounting performance (Pattij *et al.*, 2007b). Systemic administration of CB_1 receptor antagonist SR141716A (rimonabant) in rats has been found to suppresses the self-administration of many drugs of abuse (reviewed in Maldonado *et al.*, 2006), including ethanol (e.g. Cippitelli *et al.*, 2005; Economidou *et al.*, 2006) and nicotine (e.g. Cohen *et al.*, 2002); however, findings for cocaine are variable (e.g. De Vries *et al.*, 2001; Soria *et al.*, 2005). The same compound also inhibits cue-induced cocaine, nicotine and ethanol reinstatement (e.g. De Vries *et al.*, 2001; 2005; Economidou *et al.*, 2006).

Cholinergic agents

A role for cholinergic mechanisms in impulsivity is supported by the common effect of nicotine to increase impulsive action (Blondel *et al.*, 2000; Kolokotroni *et al.*, 2011) and impulsive choice (Dallery and Locey, 2005; Kolokotroni *et al.*, 2011). Recent studies indicate that these effects may be mediated by nicotinic α4β2 receptors (Tsutsui-Kimura *et al.*, 2010; Xie *et al.*, 2012a). Interestingly, nicotininc α4β2 receptor antagonists also attenuate self-administration and relapse-like behaviour to nicotine and alcohol (Watkins *et al.*, 1999; Liu *et al.*, 2007; Kuzmin *et al.*, 2009). Additionally, activity at muscarinic cholinoceptors has been found to modulate both measures of impulsivity and addiction-related behaviours. Although phasic muscarinic receptor activation appears to have no effect on impulsivity (Mirza and Stolerman, 2000; Mendez *et al.*, 2012), administration of non-selective muscarinic antagonists are reported to enhance delay discounting (Mendez *et al.*, 2012). However their effect on impulsive action is less clear with evidence for both increased (Shannon and Eberle, 2006) and decreased (Mirza and Stolerman, 2000) impulsivity on the 5-CSRTT. It is possible that variability of these findings may occur as a result of competing effects on attention (e.g. Ruotsalainen *et al.*, 2000). Other measures of behavioural inhibition such as DRL-72 and reaction time tasks, however, are generally impaired with reports of increased impulsivity (Blokland *et al.*, 2001; Jayarajan *et al.*, 2013). Interestingly, muscarinic M_1 receptor knock-out mice exhibit enhanced impulsivity on the 5-CSRTT independent of any effect on attention (Bartko *et al.*, 2011). There have also been discrepancies with the effect of muscarinic agents on drug reward and reinforcement. Non-selective muscarinic receptor agonists have been shown to reduce cocaine self-administration (Rasmussen *et al.*, 2000; Thomsen *et al.*, 2010), putatively mediated by M_1/M_4 receptors (Dencker *et al.*, 2012; Thomsen *et al.*, 2014). Interestingly, non-selective antagonism at muscarinic receptors has also been shown to reduce self-administration of methamphetamine (Davis and Smith, 1975) suggesting there may be drug and/or

receptor subtype-specific contributions of muscarinic signalling to drug reward and reinforcement.

Other neurotransmitter systems

Beyond those reviewed earlier, there is evidence for a role of other neurotransmitter systems in impulsivity and addiction-like behaviours. Despite being widely implicated in addiction (reviewed in Boutrel, 2008; Schank *et al.*, 2012), the contribution of stress-related neuropeptides to impulsive behaviour has been less well investigated. There is evidence that neurokinin 1 (NK_1) receptor antagonists reduce delay discounting (Loiseau *et al.*, 2005) as well as reduce stress-induced reinstatement of cocaine (Schank *et al.*, 2014) and alcohol (Schank *et al.*, 2011; 2014) seeking. Interestingly, however, antagonism at this receptor had no effect on cocaine (Placenza *et al.*, 2006) or alcohol reinforcement (Schank *et al.*, 2014). Neuropeptide Y, via an action at Y_2 receptors, has been reported to regulate impulsivity. Thus, Y_2 receptor knock-out mice were found to show increased impulsivity on the 5-CSRTT compared with wild-type littermates (Greco and Carli, 2006). To date, however, no studies have specifically investigated the effect of pharmacological manipulation of this system on measures of impulsivity in rodents. However, antagonism at Y_2 receptors has been shown to reduce responding for alcohol (Thorsell *et al.*, 2002; Rimondini *et al.*, 2005) although there are conflicting reports regarding this effect (Cippitelli *et al.*, 2011). Despite evidence for a role of corticotrophin releasing factor (CRF) signalling in addiction-related behaviours (reviewed in Logrip *et al.*, 2011) there is no evidence to suggest that CRF regulates impulsivity (Ohmura *et al.*, 2009).

Several other neurotransmitter systems that putatively interact with corticostriatal neurotransmission have also been implicated in both impulsivity and addiction. In this context, histamine H_3 receptors have been shown to form functional hetrodimers with both D_1 and D_2 receptors (reviewed in Ellenbroek and Ghiabi, 2014). Antagonism at histamine H_3 receptors has been reported to reduce premature responding on the 5-CSRTT (Day *et al.*, 2007) and alcohol self-administration (Lintunen *et al.*, 2001; Nuutinen *et al.*, 2011), but enhance methamphetamine self-administration (Munzar *et al.*, 2004). Similarly, adenosine A_1 receptors form heteromeric complexes within the striatum to affect neurotransmission in this region (e.g. Ciruela *et al.*, 2006). Activation of this receptor subtype has been shown to reduce impulsive responding as measured on the DRL task (Marek, 2012). Additionally, activation of this receptor inhibits dopamine-induced relapse to cocaine-seeking (Hobson *et al.*, 2013), although its effects on other drug classes has yet to be investigated.

Clinical implications

Our analysis has revealed several promising pharmacological mechanisms that bisect impulsivity and addiction-related behaviours. As drug use in impulsive individuals may represent a form of self-mediation (Khantzian, 1985) treating co-morbid impulsive symptoms may help to curb continuing drug use in addicts. While no studies to date have specifically investigated this hypothesis insights can perhaps be drawn from studies in ADHD.

With this in mind, a recent prospective study in adolescents diagnosed with ADHD and treated with methylphenidate found that rates of tobacco use were reduced when compared with a historical sample of smoking rates in a comparable, non-medicated population of individuals with ADHD (Hammerness *et al.*, 2013). However, a multi-site trial of the effect of methylphenidate treatment on rates of abstinence in individuals with ADHD and co-morbid tobacco dependence found no effect despite a reduction in ADHD symptoms (Covey *et al.*, 2011). These results plausibly suggest that treating impulsivity, at least with stimulant-based medications, may delay the development of addiction rather than remediating the active disease state once established. In keeping with this interpretation, meta-analyses suggest that stimulants protect against the development of later substance use disorders in individuals with ADHD (Wilens *et al.*, 2003), and that onset of treatment strongly predicts clinical outcome, with early initiation of treatment reducing the rate of dependence (Dalsgaard *et al.*, 2014). Clearly, much further research is needed to investigate the generality of these findings to all classes of abused drugs and whether NARIs (e.g. atomoxetine and roboxetine) offer similar protection against the development of addiction. In this regard, however, recent studies have found limited evidence for the efficacy of these drugs to enhance rates of abstinence in cocaine-dependent individuals with (Levin *et al.*, 2009) and without ADHD (Szerman *et al.*, 2005; Walsh *et al.*, 2013).

In light of enhanced rates of addiction, even in medicated ADHD patients (Hammerness *et al.*, 2013), there is naturally some concern whether exposing children and young adults to stimulant-based medications for ADHD might speed the development of later addiction. Preclinical studies have generally found that chronic pre-exposure to stimulant drugs increase subsequent levels of drug self-administration, at least in animals showing increased basal levels of impulsivity [i.e. spontaneous hypertensive rats, (Harvey *et al.*, 2011; Somkuwar *et al.*, 2013), but see Martelle *et al.* (2013); Gill *et al.* (2012); Thanos *et al.* (2007)]. However, more research is needed to understand the precise relationship between pre- and post-drug levels of impulsivity and whether in young animals stimulant exposure facilitates the development of compulsive drug self-administration, as previously described and modelled in rats (Vanderschuren and Everitt, 2004; Belin *et al.*, 2008; Pelloux *et al.*, 2012). In this regard, the reported action of atomoxetine to arrest the emergence of at least one form of compulsive behaviour in naturally impulsive rats (Ansquer *et al.*, 2014) strongly encourages further research in this area.

Conclusions

A review of the current literature highlights a number of convergent pharmacological mechanisms, which putatively mediate the reported link between impulsivity and addiction (see Table 7 for a summary). Interestingly, the available evidence suggests that while drugs capable of reducing

impulsive action often also decrease measures of addiction-related behaviours there is little convergence and often opposing effects with impulsive choice. The close alignment of pharmacological mechanisms in impulsive action and various animal addiction models suggests that they may tap into a common underlying process. Speculatively, this may involve modulatory effects on the invigoration of behaviour affecting the output of responses conditioned to food (impulsivity tasks) and drug (addiction tasks) rewards. This notion might then suggest a common involvement of mesolimbic dopamine projections, for example, to the ventral striatum, including the NAc, which are widely implicated in impulsivity (Basar *et al.*, 2010; Dalley *et al.*, 2011) and drug reinforcement (Willuhn *et al.*, 2010). Such interactions could operate at several levels including an enhancement or attenuation of appetitive approach behaviour to primary as well as conditioned reinforcing stimuli (Everitt and Robbins, 2005). Thus, the mesoaccumbens dopamine system may form the final common pathway through which other transmitter systems (for example those illustrated in Table 7) operate to modulate action impulsivity and certain drug-motivated behaviours (for reviews, see Feltenstein and See, 2013; Schmidt and Weinshenker, 2014). Conceivably, this mechanism may encompass dopamine-mediated gating of cortico-accumbens projections from the PFC, amygdala, and hippocampus (Goto and Grace, 2008), and thereby the expression of drug craving and relapse (Kalivas and Volkow, 2011). Interestingly, while our analysis has revealed a close relationship between motoric forms of impulsivity and addiction-related behaviours, there is little evidence for a similar association with impulsive choice, with the exception of nicotinic α4β2 receptor antagonists, which decrease both action- and choice-related forms of impulsivity and drug-seeking responses. The apparently weak association between choice impulsivity and addiction-related behaviours suggest they may involve distinct pharmacological substrates. Nevertheless, there is some evidence that NARIs may be efficacious in several forms of impulsivity, including delay-discounting impulsivity; however, larger-scale prospective studies are needed to investigate whether early intervention in ADHD (e.g. with NARIs) significantly moderates the risk of addiction in adulthood. Finally, research is needed to explore emerging neurotransmitter substrates and mechanisms (e.g. GABA, glutamate, cannabinoids and ACh) as a strategy to develop more effective therapies in addiction and impulsivity disorders.

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Author contributions

B. J. developed the review concept, wrote and edited the paper J. W. D. edited the paper, provided feedback during the drafting process and assisted in developing the review concept.

Table 7

Pharmacological interventions that reduce both impulsivity and addiction-like behaviour in rodent models

Neurotransmitter system	Impulsive action	Impulsive choice
Dopaminergic	D_1 antagonist	
5-hydroxytryptaminergic	SSRI	
	$5\text{-}HT_{2A}$ antagonist*	
	$5\text{-}HT_{2A/C}$ antagonist	
	$5\text{-}HT_{2C}$ agonist	
	$5\text{-}HT_{2B/C}$ agonist	
	$5\text{-}HT_3$ antagonist	
Adrenergic	NARI	
	NSRI*	
	α_1 antagonist	
	β antagonist	
Glutamate		$mGlu_1$ antagonist
Cannabinoid	CB_1 antagonist	
Cholinergic	Nicotinic α4β2 antagonist	Nicotinic α4β2 antagonist

*Evidence to suggest effect in relapse-like behaviour, but not self-administration, despite the apparent relationship of both to impulsivity.
NSRI, noradrenaline 5-HT re-uptake inhibitor; SSRI, selective 5-HT re-uptake inhibitor.

Conflict of interest

None.

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