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REVIEW

The utility of rat models of impulsivity in developing pharmacotherapies for impulse control disorders

Catharine A Winstanley

Department of Psychology, University of British Columbia, Vancouver, BC, Canada

Correspondence
Catharine A Winstanley, Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC V6T 1Z4, Canada. E-mail: cwinstanley@psych.ubc.ca

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High levels of impulsive behaviours are a clinically significant symptom in a range of psychiatric disorders, such as attention deficit hyperactivity disorder, bipolar disorder, personality disorders, pathological gambling and substance abuse. Although often measured using questionnaire assessments, levels of different types of impulsivity can also be determined using behavioural tests. Rodent analogues of these paradigms have been developed, and similar neural circuitry has been implicated in their performance in both humans and rats. In the current review, the methodology underlying the measurement of different aspects of impulsive action and choice are considered from the viewpoint of drug development, with a focus on the continuous performance task (CPT), stop-signal task (SST), go/no-go and delay-discounting paradigms. Current issues impeding translation between animal and human studies are identified, and comparisons drawn between the acute effects of dopaminergic, noradrenergic and serotonergic compounds across species. Although the field could benefit from a more systematic determination of different pharmacological agents across paradigms, there are signs of strong concordance between the animal and human data. However, the type of impulsivity measured appears to play a significant role, with the SST and delay discounting providing more consistent effects for dopaminergic drugs, while the CPT and SST show better predictive validity so far for serotonergic and noradrenergic compounds. Based on the available data, it would appear that these impulsivity models could be used more widely to identify potential pharmacotherapies for impulse control disorders. Novel targets within the glutamatergic and serotonergic system are also suggested.

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Abbreviations
5CSRT, five-choice serial reaction time task; 5-HT, serotonin; ADHD, attention deficit hyperactivity disorder; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BART, Balloon Analogue Risk Task; BD, bipolar disorder; BIS-11, 11-point Barratt Impulsiveness Scale; BPD, borderline personality disorder; CPT, continuous performance task; DA, dopamine; DAT, dopamine transporter; ICD, impulse control disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; IGT, Iowa Gambling Task; mGluR, metabotropic glutamate receptor; mPFC, medial prefrontal cortex; NA, noradrenaline (norepinephrine); OCD, obsessive–compulsive disorder; PAM, positive allosteric modulator; PG, pathological gambling; SSRI, serotonin selective reuptake inhibitor; SSRT, stop signal reaction time; SST, stop-signal task

Impulsivity and impulse control disorders

Impulsivity can be broadly defined as acting, or making decisions, without appropriate forethought, thereby enhancing the potential for negative consequences. A healthy level of impulsivity can be a beneficial aspect of our character, enabling us to seize opportunities and gain valuable new experiences. However, high levels of impulsivity are socially unacceptable, and can be personally and financially costly. In terms of psychiatric diagnoses, deficits in impulse control are

a key symptom in both attention deficit hyperactivity disorder (ADHD) and the manic episodes inherent within bipolar disorder (BD), and can also be a feature of borderline personality disorder (BPD). The 4th edition of the Diagnostic and Statistical Manual (text revision) also identifies a diverse group of psychiatric illnesses, collectively characterized as impulse control disorders (ICDs) not elsewhere classified, which include pathological gambling (PG), trichotillomania, intermittent explosive disorder, kleptomania and pyromania. Likewise, the World Health Organization's International Classification of Diseases (ICD-10) includes a diverse category of habit and impulse disorders (F63) which encompasses the same collection of illnesses. Furthermore, it is increasingly recognized that impulsivity is a vulnerability factor for substance abuse, and may facilitate relapse to drug-seeking and treatment failure (Jentsch and Taylor, 1999; Moeller *et al.*, 2001b; Winstanley *et al.*, 2010a). There is a significant need for better treatments for many of these disorders, as current pharmacotherapies can be poorly tolerated or ineffectual. Modelling the full manifestation of such mental illnesses in animals is clearly impossible. However, animal models are an essential component of any pharmaceutical research and development. The fact that the core symptom of impulsivity can be measured in laboratory animals could therefore be of great utility.

However, it has become clear that there are many forms of impulse control, and that the term 'impulsivity' encompasses a range of behaviours from motor disinhibition to maladaptive decision-making (Brunner and Hen, 1997; Evenden, 1999; Moeller *et al.*, 2001a). The disparate nature of these impulsive behaviours has lead researchers in the field to question the viability of the impulsivity construct. However, the non-unitary nature of impulse control is not at all unusual when considering other psychological processes (Winstanley *et al.*, 2010a). For example, memory, learning and attention can all be subdivided into distinct forms (declarative vs. procedural memory, associative vs. non-associative learning, sustained vs. divided attention, etc.), but this does not render obsolete the use of a singular umbrella term with which to describe them.

Questionnaires which assess multiple aspects of impulsivity, such as the 11-point Barratt Impulsiveness Scale (BIS-11), the Impulsivity Rating Scale (IRS) or the Karolinska Scale of Personality, are commonly used clinically (see Evenden, 1999 for discussion). The results of such studies consistently indicate that deficits in many types of impulsivity coexist in psychiatric populations, and using behavioural tests to assess more than one impulsive behaviour has been shown to increase the accuracy of psychiatric diagnosis (Solanto *et al.*, 2001). It is also quite well-established that individuals may have a primary deficit in one particular aspect of impulse control, and this may lead to the definition of subclasses of a illness such as in ADHD which may respond differently to drug treatments (Sonuga-Barke, 2003). Indeed, perhaps the biggest challenge in treating any psychiatric disorder, including ICDs, is understanding the influence of individual difference or trait variables on treatment outcome. One future, albeit far-off, goal could be to tailor drug prescriptions to fit the subject's exact symptom profile, rather than assuming a generic approach based on a broad diagnosis. In this respect, valid models of different aspects of impulsivity may ultimately be a help rather than a hindrance in identifying potential clinical utility of novel compounds, particularly if they can capture the influence of environmental factors on behaviour. In pursuing the potential application of a drug for treatment of high levels of impulsivity, it is therefore becoming increasingly apparent that multiple domains of impulsive behaviour should be measured.

Fractionating impulsivity: from humans to animals

As may be expected when attempting to divide a broad concept such as impulsivity into distinct entities, there is some variation between what types of impulsivity should be considered both unique and representative of the construct (see Evenden, 1999; Winstanley *et al.*, 2010a for discussion). Factor analysis of self-report questionnaires such as the BIS-11 suggest three major dimensions of impulsivity: motor, non-planning and attentional (Patton *et al.*, 1995; Moeller *et al.*, 2001a). The attentional/cognitive domain is reflective of the degree to which an individual can focus on the task at hand or tolerate cognitive complexity, the motor component reflects spontaneity or action without due consideration, whereas non-planning impulsivity reflects a lack of regard for the future. In translating these subjective measurements into objective behavioural tests which can be adapted across species, the attentional dimension has been the most problematic to isolate; 'cognitive complexity' overlaps with a broad range of executive functions, and the extent to which the allocation of cognitive effort overlaps with impulse control is currently unclear. However, attempts to model both motor and non-planning impulsivity have been more fruitful, and the remainder of this review will focus on these domains.

Behavioural models of motor impulsivity

The stop-signal task (SST), the go/no-go task and the continuous performance task (CPT) are the most commonly used behavioural tests of motor impulsivity in the assessment of clinical populations. In all of these paradigms, the subject is required to withhold from making a prepotent motor response. However, there are some seemingly minor, yet structurally significant, differences between them. In the SST, the individual is required to respond as fast as possible to a particular target (see Verbruggen and Logan, 2009 for review). On a subset of trials, a stop signal is presented at varying delays after this go signal, and the subject must then cancel their planned response. The greater the delay between the stop and go signals, and therefore the closer the timing of the stop signal to the mean go response time, the more difficult it becomes to withhold from making the go response. It is possible to estimate the stop signal reaction time (SSRT) based on the subjects' mean go reaction time and their ability to inhibit responding at different stop signal delays (see Logan, 1994 for details of the horse-race model used for this calcu-

lation). The SSRT therefore indicates how capable the subject is of cancelling an action once it has already been initiated.

Although go/no-go paradigms likewise use two signals, one indicating that a go response is required, and the other that this response should be inhibited, only one signal is presented on any trial (e.g. Hogg and Evans, 1975). The go signal is considerably more frequent, thereby priming the motor response, but the signal occurs at the beginning of each trial, before any action has been initiated. Hence, in a go/no-go task, the subject must withhold from responding until the go signal is detected, whereas in the SSRT, the subject must always initiate the go response but inhibit its completion if the stop signal is detected. Both SST and go/no-go tasks have been developed for use in rodents and non-human primates (SST: Feola *et al.*, 2000; Eagle and Robbins, 2003; Liu *et al.*, 2009; go/no-go: Iversen and Mishkin, 1970; Terman and Terman, 1973). Data from both human and animal models indicate that the types of inhibition taxed by these tasks – action cancellation in the SST, and action restraint in the go/no-go – can be dissociated both in terms of the supporting neural circuitry and the pharmacology of their regulation (Rubia *et al.*, 2001; Eagle *et al.*, 2008; Eagle and Baunez, 2010).

The CPT is very different in design to the other two tasks, in that subjects are required to scan a 5-digit sequence and respond when the numbers match a target stimulus. 'False alarm' errors occur when the subject responds positively to a sequence which is identical to the target, with the exception of the final number (Rosvold *et al.*, 1956; Wilkinson, 1963). When making such errors, the subject responds prematurely before processing the full sequence. To avoid making such impulsive responses, the subject therefore needs to wait for the correct signal. The five-choice serial reaction time task (5CSRT) was designed as a rodent analogue of this task, and provides somewhat independent measures of attention and motor impulsivity (Carli *et al.*, 1983). The visual stimulus is a simple cue light rather than a complex series of digits, but the cue can be presented in any one of five spatial locations, and is only illuminated for a very brief time period. The rat is required to respond at the correct location in order to earn food reward. Responses made prematurely, before the light has been presented, provide a reliable index of a rat's inability to wait for the correct stimulus and are thought analogous to the errors of commission made on the CPT. Compared to the other models of impulsive action, the surface structure of the 5CSRT probably deviates the most from the clinical test it is based on. Nevertheless, the neural circuitry and neurochemistry underlying performance of the CPT and 5CSRT suggest a fair degree of correlation between the two species-dependent paradigms (Robbins, 2002).

Action restraint is required in order to both inhibit the go response in the go/no-go and to withhold from responding to an incorrect target in the CPT. However, in the former, the subject is required to 'reset' the go response when the no-go cue is presented, whereas in the latter the subject must simply refrain from responding until the correct cue is presented. As such, there may well be a distinction within action restraint between waiting and resetting (Winstanley *et al.*, 2010a), and differences have certainly been observed in the outcomes of experiments using the 5CSRT and go/no-go paradigms (see sections on *The DA system*, *The NA system* and *The 5-HT system*).

Behavioural models of 'non-planning', or impulsive decision-making

Despite the plethora of tasks that have been developed to study behavioural disinhibition, there are relatively few which selectively target aspects of impulsive decision-making, or non-planning impulsivity. Delay-discounting tasks have probably been the most successful in terms of modelling the inability to prioritize future rewards over satisfying the need for more immediate gratification (Ainslie, 1975). Every reward loses some of its subjective appeal as the delay to its delivery increases; that is, the delay discounts its value. In delay-discounting paradigms, subjects choose between smaller rewards available immediately versus larger rewards available after a varying delay. Individuals which generate steeper discounting curves, such that each unit of time-delay has a greater negative effect on the valuation of the reward, are described as more impulsive on this measure. The majority of delay-discounting data from human subjects has been obtained using a questionnaire involving hypothetical choice between two fictional rewards, as per Rachlin's original studies (Rachlin *et al.*, 1991). Following concern regarding the ability of such judgements to reflect real-world decisions (e.g. Bickel and Marsch, 2001), subjects are often informed that one of their choices will be picked at random and honoured by the experimenter (i.e. if a subject chooses $20 in 2 weeks over $5 in 3 days, that payment is mailed to them within the appropriate time frame). Experiential delay-discounting tasks have also been developed, in which subjects receive delays and rewards in real time, and which can be more sensitive to acute pharmacological manipulations (Reynolds and Schiffbauer, 2004; Reynolds *et al.*, 2006). However, the higher levels of impulsive choice observed using such experiential delay-discounting tasks have likewise led to questions over their validity (see Madden and Johnson, 2008 for discussion), and the majority of studies still use variants of the questionnaire method.

Given the debate regarding the most valid measurement of delay discounting in human subjects, it is perhaps unsurprising to discover that numerous delay-discounting paradigms have likewise been developed in rats. None of these paradigms is an exact analogue of the methodology used most frequently in humans. Nevertheless, as with the human data, there is a general concordance in the output in that nearly all variants of the task can distinguish high and low impulsive subgroups, and can be used to estimate a delay-discounting curve. However, the paradigms also vary considerably in terms of equipment used (operant chamber vs. T-maze) and the task structure (adjusting vs. set delays, within vs. between session shifts in delay, relative size of large vs. small reward, etc.). Although seemingly superficial, these differences in methodology can be a crucial factor in influencing drug effects (see Winstanley, 2010; Winstanley *et al.*, 2010a for details of these issues). Discussion of the pharmacological effects on such behaviour will therefore be restricted to findings obtained using a paradigm which was deliberately developed with drug-testing in mind, namely that first published by Evenden and Ryan (1996), although similar effects have also been observed with other paradigms. This task includes a within-session, rather than a between-session, shift

in delays such that a delay-discounting curve can be obtained from each challenge session. This is not to say that other models have not provided the field with valuable information regarding the neurobiology underlying the discounting process, or that the Evenden and Ryan task is not without pitfalls, but some consistency in methodology must be present for our comparisons to be meaningful. The analysis will also only consider data in which a cue light was NOT used to bridge the delay, as this additional stimulus can also have significant effects on discounting rate (Cardinal *et al.*, 2000; Zeeb *et al.*, 2010).

Issues pertaining to the validity of the comparison between clinical and preclinical data sets

In the final section before we review the specific effects of various compounds on impulsivity, let us briefly consider issues pertaining to the relevance of those comparisons. By comparing the behavioural effects of targeted infusion of pharmacological agents and neurotoxins in rodents, to findings from neuroimaging and the neuropsychological assessment of brain-damaged patients, the majority of data indicate that similar neural circuitry controls these impulsive behaviours across species. Key areas include the orbitofrontal and medial prefrontal cortices (mPFC), the nucleus accumbens and the subthalamic nucleus. Such homogeneity is important in determining the validity of any animal model, and there have been a number of recent reviews summarizing this literature (Oquendo and Mann, 2000; Dalley *et al.*, 2004; Winstanley *et al.*, 2006; Eagle *et al.*, 2008; Eagle and Baunez, 2010). Although target discovery and validation studies can be informed by direct intra-cerebral application of compounds, the current review will focus on the effects of systemically administered pharmacological agents, as these are probably the most relevant data sets with regards to screening and proof-of-concept studies in drug development.

In the following subsections, drugs have been grouped together according to which neurotransmitter system they target. Given both the current and historical importance of the monoamine systems in the treatment of ICDs, most of the pharmacological data available in both human and animal subjects concerns compounds which affect the serotonin (5-HT), dopamine (DA) and noradrenaline (NA) systems. One issue worth noting is that much of the research conducted using rodent models of impulse control is aiming to elucidate the biological basis of impulsive behaviours, rather than whether a particular compound has therapeutic potential in treating ICDs. These two aims are not mutually exclusive, but the experimental designs that would be employed to resolve such questions are not necessarily identical. For example, if an experimenter wishes to determine whether DA transmission via D_2 receptors plays a role in a particular aspect of impulse control in a rodent model, they may evaluate the effects of a counterbalanced series of intermittent injections of different doses of a D_2 receptor antagonist and vehicle, administered just prior to the performance of the behavioural task. However, if a D_2 receptor antagonist was to be tested for therapeutic efficacy in a proof-of-concept study or clinical trial, the compound would be given once or twice a day to patients with an ICD, and dosing repeated for a number of weeks during which symptoms would be assessed at set time points. Such assessments often involve symptom ratings questionnaires rather than behavioural tests, and the time of drug administration is not necessarily proximal to the time at which symptoms are evaluated. The differences in these designs lead to a number of issues which should be explicitly acknowledged.

Firstly, the fact that human behavioural models are often not used in drug development, despite their methodological advantages compared to questionnaires (Moeller *et al.*, 2001a), can impede attempts to estimate the utility of animal models for this research purpose. Secondly, extrapolating from acute administration in an animal model to the effects of chronic administration in humans confounds differences in dosing regimen as well as species. Data from acute administration in normal rats and humans should also be compared when determining the validity of an animal model. From a drug development perspective, positive effects of acute administration are certainly informative, in that an immediate onset of therapeutic action is always desirable. However, it is inevitable that any successful treatment would need to be given repeatedly, with the ensuing danger of tolerance or sensitization, yet few preclinical studies which are published report the *behavioural* effects of chronic or slow-release formulations of anti-impulsivity drugs. This is more common in studies of antipsychotic and antidepressant medications (e.g. Gao *et al.*, 1997; 1998; Malberg *et al.*, 2000; Frost *et al.*, 2004; D'Sa *et al.*, 2005), presumably because of the delay to onset of their clinical effects. It would be incredibly useful if the effects of repeated administration of anti-impulsivity medications, using mini-pumps or daily injections, over at least 2–3 weeks were reported on different behavioural tests of impulse control, in that such data would allow better comparisons between human and animal studies.

The third issue regarding the use of a patient population versus healthy controls is seemingly impossible to address: the cause of many ICDs is unknown, either from an environmental or genetic perspective, and whether a psychiatric disorder can ever fully be made manifest in a non-human subject is a matter of some debate. However, it is also worth noting that many ICDs, and other mental illnesses, are dimensional rather than categorical in nature, and there extends a continuum in symptom occurrence and severity between the healthy and patient populations. Increasing levels of aberrant behaviour or cognitions which lie below the clinical threshold can sometimes be indications that a clinical episode is imminent. Although use of a disease model may not be a practical requirement for the validity of animal testing, an increasing number of studies are considering individual differences in impulsive behaviour to be an important factor, and one that seems to significantly affect the response to drug challenges (e.g. Poulos *et al.*, 1995; Feola *et al.*, 2000; Dalley *et al.*, 2007; Perry *et al.*, 2008; Zeeb *et al.*, 2010). However, the majority of data published to date concern the behavioural effects of acute compounds on a heterogeneous group of rats, with no consideration of baseline differences in impulse control. It is worth noting that research into impulsivity and treatments for ICDs is not unusual in regards to the presence of these confounds. Nonetheless, if individual

differences within the normal population were taken into account (e.g. in a regression or covariate analysis), it may be possible to identify compounds which have maximal effect on subjects with naturally higher levels of baseline impulsivity. In that this may reflect a dimensional endophenotype, such results may model the drug response in subjects 'vulnerable' to ICDs.

Hence, the question we will aim to address in the following discussion has become twofold: (i) Does acute drug treatment in an animal model of impulsive behaviour produce the same effects as acute treatment in healthy volunteers? (ii) Is this acute treatment effect informative when predicting whether a compound will have therapeutic effects in the relevant patient population? The effects of different compounds on the behavioural tests of impulsivity identified above are provided in Tables 1–3 for ease of reference, not only in terms of identifying similarities or differences across species, but also to demonstrate what has and has not been tested to date.

The DA system

Dysfunction within the DA system has been hypothesized to play a major role in psychiatric disorders such as ADHD (Ernst *et al.*, 1998; Faraone and Biederman, 1998; Dougherty *et al.*, 1999; Krause *et al.*, 2000) and PG (Goudriaan *et al.*, 2004; Voon *et al.*, 2009), in which impulsivity is high. Similarly, aberrant DA signalling has been suggested to contribute to the deficits in impulse control associated with drug addiction (Jentsch and Taylor, 1999; Dalley *et al.*, 2007; Lee *et al.*, 2009). Psychostimulants, such as amphetamine (Adderall™) and methylphenidate (Ritalin™, Concerta™), form the first line of treatment for ADHD. Beneficial effects of these compounds on impulsivity as assessed by the CPT (Brown *et al.*, 1986; Klorman *et al.*, 1991; Losier *et al.*, 1996; Aggarwal and Lillystone, 2000; Riccio *et al.*, 2001), SST (Tannock *et al.*, 1989; Aron *et al.*, 2003), go/no-go (Vaidya *et al.*, 1998) and delay-discounting paradigm (Shiels *et al.*, 2009) have been established in this patient population. Although these drugs affect multiple neurotransmitter systems, their therapeutic efficacy is thought to arise largely from their effects on DA (e.g. Tripp and Wickens, 2009).

In healthy volunteers, acute administration of both amphetamine and methylphenidate has been shown to decrease impulsivity in all four paradigms (Table 1A: Rapoport *et al.*, 1978; Sostek *et al.*, 1980; Weingartner *et al.*, 1980; Klorman *et al.*, 1983; Barkley *et al.*, 1991; Losier *et al.*, 1996; Vaidya *et al.*, 1998; de Wit *et al.*, 2000; 2002; Fillmore *et al.*, 2003; Wilson *et al.*, 2006; Overtoom *et al.*, 2009; Shiels *et al.*, 2009; Li *et al.*, 2010). Data from rodent studies has been somewhat less consistent (Table 1B) despite the use of similar drug doses and routes of administration, although it should be noted that negative or contrasting effects have also been seen in the human population following administration of these drugs (Overtoom *et al.*, 2003; Acheson and de Wit, 2008; Vansickel *et al.*, 2008). However, these null effects seem largely attributable to either an insufficient dose of compound (Overtoom *et al.*, 2003), or variation in the behavioural baselines that prevented detection of improvements (Acheson and de Wit, 2008; Vansickel *et al.*, 2008), again indicating the importance of basal levels of motor impulsivity when considering drug effects.

In contrast to findings from the CPT, both amphetamine and methylphenidate reliably increase premature responding in rats performing the 5CSRT (Cole and Robbins, 1987;

Table 1A

The effects of acute administration of dopaminergic compounds on different tests of impulsivity in humans

Drug	CPT Study	↑ – ↓	SST Study	↑ – ↓	Go/no-go Study	↑ – ↓	Delay discounting Study	↑ – ↓
Amphetamine	Rapoport *et al.*, 1978 Sostek *et al.*, 1980 Weingartner *et al.*, 1980	↓	de Wit *et al.*, 2000 de Wit *et al.*, 2002	↓	Fillmore *et al.*, 2003[2]	↑	de Wit *et al.*, 2002	↓
			Acheson and de Wit, 2008	–	de Wit *et al.*, 2002	↓		
Methylphenidate	Klorman *et al.*, 1983[1] Losier *et al.*, 1996[1] Barkley *et al.*, 1991[1]	↓	Overtoom *et al.*, 2009 Li *et al.*, 2010[2]	↓	Vaidya *et al.*, 1998 Wilson *et al.*, 2006[1]	↓	Shiels *et al.*, 2009	↓
			Overtoom *et al.*, 2003[1]	–	Vansickel *et al.*, 2008[2]	–		
Cocaine	Herning *et al.*, 1987	–	Fillmore *et al.*, 2006	↓	Fillmore *et al.*, 2005[2]	↓	???	?
L-DOPA	???	?	Overtoom *et al.*, 2003[1]	–	Hershey *et al.*, 2004	–	Pine *et al.*, 2010	↑
Pramipexole	???	?	???	?	Hamidovic *et al.*, 2008	–	Hamidovic *et al.*, 2008	–

↑: increase in impulsivity; ↓: decrease in impulsivity; –: no change in impulsivity. Pharmacological mechanisms of action of the drugs listed: amphetamine, cocaine, methylphenidate: psychostimulant; L-DOPA: dopamine precursor; pramipexole: $D_{2/3}$ receptor agonist.
[1]Subject population was diagnosed with ADHD.
[2]Subject population was diagnosed with cocaine abuse.

Table 1B

The effects of acute administration of dopaminergic compounds on different tests of impulsivity in rats

Drug	5CSRT Study	↑ – ↓	SST Study	↑ – ↓	Go/no-go Study	↑ – ↓	Delay discounting Study	↑ – ↓
Amphetamine	Cole and Robbins, 1987 Harrison *et al.*, 1997 Van Gaalen *et al.*, 2006a Pattij *et al.*, 2007 van Gaalen *et al.*, 2009 Loos *et al.*, 2010[m]	↑	Eagle and Robbins, 2003 Eagle *et al.*, 2009 Feola *et al.*, 2000	↓	Loos *et al.*, 2010[m]	–	Evenden and Ryan, 1996 Cardinal *et al.*, 2000 Stanis *et al.*, 2008	↑
							Winstanley *et al.*, 2003b Winstanley *et al.*, 2005 Van Gaalen *et al.*, 2006b	↓
Methylphenidate	Milstein *et al.*, 2010 Navarra *et al.*, 2008b	↑	Eagle *et al.*, 2007	↓	???	?	Van Gaalen *et al.*, 2006b	↓
Cocaine	Van Gaalen *et al.*, 2006a Winstanley *et al.*, 2007	↑	???	?	Paine and Olmstead, 2004	↑	Winstanley *et al.*, 2007	↓
GBR 12909	Van Gaalen *et al.*, 2006a	↑	Bari *et al.*, 2009 Loos *et al.*, 2010[m]	↑	???	?	Van Gaalen *et al.*, 2006b	↓
D_1 agonist	Winstanley *et al.*, 2010b	↓	???	?	???	?	???	?
D_1 antagonist	Harrison *et al.*, 1997	↓	???	?	???	?	Van Gaalen *et al.*, 2006b	↑
	Van Gaalen *et al.*, 2006a	–						
D_2 agonist	Winstanley *et al.*, 2010b	↓	???	?	???	?	???	?
D_2 antagonist	Harrison *et al.*, 1997[a] Van Gaalen *et al.*, 2006a[c] van Gaalen *et al.*, 2009[d]	–	???	?	???	?	Evenden and Ryan, 1996[b] Van Gaalen *et al.*, 2006b[c]	–
D_3 agonist	???	?	???	?	???	?	van den Bergh *et al.*, 2006	–
D_3 antagonist	van Gaalen *et al.*, 2009	–	???	?	???	?	???	?
D_4 antagonist	Milstein *et al.*, 2010	–	???	?	???	?	???	?
Mixed $D_{1/2}$ antagonist	Koskinen and Sirvio, 2001 Baunez and Robbins, 1997	↓	Eagle *et al.*, 2007	–	Eagle *et al.*, 2007	–	Cardinal *et al.*, 2000 Winstanley *et al.*, 2003b	↑ –

↑: increase in impulsivity; ↓: decrease in impulsivity; –: no change in impulsivity. Pharmacological mechanisms of action of the drugs listed: amphetamine, cocaine, methylphenidate: psychostimulant; GBR12909: DAT blocker; D_1 receptor agonist: SKF 81297; D_1 receptor antagonist: SCH23390; D_2 receptor agonist: quinpirole; D_2 receptor antagonist: sulpiride[a], haloperidol[b], eticlopride[c], L-741,626[d]; D_3 receptor agonist: 7-OH-DPAT; D_3 receptor antagonist: SB-277011; D_4 receptor antagonist: L-745,870; $D_{1/2}$ receptor antagonist: cis-z-flupenthixol. [m] = subjects were mice rather than rats.

Harrison *et al.*, 1997; Pattij *et al.*, 2007; Milstein *et al.*, 2010; Navarra *et al.*, 2008b; van Gaalen *et al.*, 2009). Little data is available regarding their effects on the go/no-go task, but see Loos *et al.* (2010) for null data in mice. More complementary to the human data are observations that both stimulants improve inhibitory control on the rat version of the SST (Feola *et al.*, 2000; Eagle and Robbins, 2003; Eagle *et al.*, 2007; 2009), and increase choice of larger delayed rewards in the rat delay-discounting paradigm (Winstanley *et al.*, 2003b; 2005; van Gaalen *et al.*, 2006b), although amphetamine has also been reported to have the opposite effect on the latter task (Evenden and Ryan, 1996; Cardinal *et al.*, 2000; Stanis *et al.*, 2008) – see Winstanley *et al.* (2003b) and Winstanley (2010) for discussion of methodological issues pertaining to these discrepant findings. Although not considered as a therapeutic agent, cocaine has been reported to have generally similar effects to amphetamine on these different forms of impulsivity in the rat (Paine and Olmstead, 2004; van Gaalen *et al.*, 2006a,b; Winstanley *et al.*, 2007). Likewise, cocaine has been found to decrease SSRT (Fillmore *et al.*, 2006) and reduce impulsivity on the go/no-go task in human subjects (Fillmore *et al.*, 2005), although the latter report used stimulant-dependent subjects. No changes have been observed following cocaine administration on the go/no-go task (Herning *et al.*, 1987).

In terms of the pharmacology underlying the effects of these psychostimulants, it has been repeatedly demonstrated that blockade of DA's actions, particularly D2-like receptors, can prevent amphetamine from increasing premature responding on the 5CSRT (Cole and Robbins, 1989; van Gaalen *et al.*, 2006a; 2009; Pattij *et al.*, 2007). Furthermore, the selective DA transporter (DAT) inhibitor, GBR 12909, has similar effects to amphetamine in terms of increasing impulsivity on the 5CSRT but decreasing impulsive choice on the delay-discounting task (van Gaalen *et al.*, 2006a,b). However, opposite effects of this drug and amphetamine are observed on the SST (Bari *et al.*, 2009; Loos *et al.*, 2010). Furthermore, administration of the DA precursor L-DOPA increases impulsive choice (Pine *et al.*, 2010) in human volunteers, but does not affect SST or go/no-go performance (Overtoom *et al.*, 2003; Hershey *et al.*, 2004). Acute administration of prami-

pexole also does not affect go/no-go or delay-discounting performance in healthy control subjects (Hamidovic *et al.*, 2008). Collectively, these data suggest that amphetamine's actions cannot be reproduced by increasing DA levels.

Following on from these human data, the effects of selective agonists or antagonists do not appear to model amphetamine's effects in rats; both D_1 and D_2 agonists decreased premature responding on the 5CSRT (Winstanley *et al.*, 2010b), whereas administration of selective D_2, D_3 and D_4 antagonists do not modulate any form of impulsivity tested (Evenden and Ryan, 1996; Harrison *et al.*, 1997; van den Bergh *et al.*, 2006; van Gaalen *et al.*, 2006a,b; 2009; Milstein *et al.*, 2010). However, the D_1 antagonist SCH 23390 and the mixed $D_{1/2}$ antagonist flupenthixol can induce some of the opposite effects to amphetamine, decreasing impulsivity on the 5CSRT while increasing choice of the small immediate reward on the delay-discounting paradigm (Baunez and Robbins, 1997; Cardinal *et al.*, 2000; Koskinen and Sirvio, 2001).

One obvious conclusion to draw from these observations is that a DA releaser, or reuptake inhibitor, 'potentiates' DA's effects in a very different manner from a DA agonist. Understanding exactly what this mechanism might be, either in terms of pharmacokinetics or changes in intracellular signalling pathways, might significantly advance our understanding of how pathology within the DA system may lead to ICDs, and why stimulant drugs appear to improve it. For example, it has recently been shown that both amphetamine and cocaine can decrease hyperactivity in the DAT-cocaine-insensitive mouse, a potential model of ADHD, by enhancing striatal DA and normalizing aberrant D_1-mediated signalling (Napolitano *et al.*, 2010).

As mentioned above, high impulsivity, both in terms of impulsive action and impulsive choice (Winstanley *et al.*, 2010a), is thought to be a major risk factor for developing substance abuse. Certainly, both current and recently abstinent drug users have been shown to be more impulsive on the SST (Fillmore and Rush, 2002; Li *et al.*, 2006; 2008) and go/no-go tasks (Lane *et al.*, 2007), as well as tests of impulsive decision-making (Kirby *et al.*, 1999; Monterosso *et al.*, 2001; Bornovalova *et al.*, 2005). Furthermore, high levels of motor impulsivity are associated with low levels of treatment compliance in cocaine addiction (Moeller *et al.*, 2001b), and a significant proportion of drug users relapse 'on impulse', with no premeditation. In addition to correlational studies indicating that drug users are more impulsive, data from animal studies also indicate that high motor impulsivity, as assessed by the 5CSRT, predicts the development of addiction in rats, and that withdrawal can precipitate increases in this form of impulsivity (Dalley *et al.*, 2007; Belin *et al.*, 2008; Economidou *et al.*, 2009; Winstanley *et al.*, 2009). Treatments which could reduce aspects of impulsivity in substance abusers could therefore be of significant clinical interest. However, stimulant medications are clearly unlikely to ever be approved for this patient group given the abuse potential, although data from both human (SSRT) and rat (5CSRT) studies indicate that cocaine-experienced subjects can either become less impulsive after cocaine or methylphenidate administration (Fillmore *et al.*, 2006; Dalley *et al.*, 2007; Li *et al.*, 2010) or are tolerant to the pro-impulsive effects of cocaine (rat, 5CSRT: Winstanley *et al.*, 2007). Non-dopaminergic drugs may offer more hope for such a clinical application.

In summary, findings from the SST and delay-discounting paradigms appear to be the most consistent between rats and humans when considering dopaminergic drugs, although much of this literature concerns psychostimulants which affect multiple transmitter systems. Given that DA agonists have not so far been found to reproduce these effects, the opportunity exists to use animal models of impulsivity to investigate the mechanisms by which stimulant medications improve impulse control.

The NA system

A summary of the acute effects of noradrenergic compounds on different tests of impulsive behaviour can be found in Table 2A (humans) and Table 2B (rats). Despite the fact that much of the ADHD literature is still dominated by research

Table 2A

The effects of acute administration of noradrenergic compounds on different tests of impulsivity in humans

Drug	CPT Study	↑ – ↓	SST Study	↑ – ↓	Go/no-go Study	↑ – ↓	Delay discounting Study	↑ – ↓
Atomoxetine	Barry *et al.*, 2009[1]	↓	Chamberlain *et al.*, 2006	↓	???	?	???	?
Bupropion	Conners *et al.*, 1996[1]	↓	Acheson and de Wit, 2008	–	???	?	???	?
Desipramine	Singer *et al.*, 1995[2]	–	Overtoom *et al.*, 2003[1]	↓	???	?	???	?
Guanfacine	Chappell *et al.*, 1995 Scahill *et al.*, 2001	↓	Muller *et al.*, 2005	–	???	?	???	?
Clonidine	Singer *et al.*, 1995	–	???	?	???	?	???	?
Yohimbine	Swann *et al.*, 2005	↑	???	?	???	?	???	?

↑: increase in impulsivity; ↓: decrease in impulsivity; –: no change in impulsivity. Pharmacological mechanisms of action of the drugs listed: atomoxetine: NA reuptake inhibitor; bupropion: DA-NA reuptake inhibitor; desipramine: NA-5-HT reuptake inhibitor; guanfacine: α_2 agonist; clonidine: α_2 agonist.

[1]Subject population was diagnosed with ADHD.

[2]Subject population was diagnosed with ADHD and Tourette's Syndrome.

Table 2B

The effects of acute administration of noradrenergic compounds on different tests of impulsivity in the rat

Drug	5CSRT Study	↑ – ↓	SST Study	↑ – ↓	Go/no-go Study	↑ – ↓	Delay discounting Study	↑ – ↓
Atomoxetine	Robinson *et al.*, 2008 Navarra *et al.*, 2008b Tsutsui-Kimura *et al.*, 2009 Blondeau and Dellu-Hagedorn, 2007	↓	Robinson *et al.*, 2008 Bari *et al.*, 2009	↓	???	?	Robinson *et al.*, 2008	↓
Bupropion	???	?	???	?	???	?	???	?
Desipramine	Van Gaalen *et al.*, 2006a	↓	???	?	???	?	Van Gaalen *et al.*, 2006b	–
Milnacipran	Tsutsui-Kimura *et al.*, 2009	↓	???	?	???	?	???	?
Guanfacine	Milstein *et al.*, 2007	↓	Bari *et al.*, 2009	↑	???	?	???	?
Clonidine	???	?	???	?	???	?	Van Gaalen *et al.*, 2006b	↑
Yohimbine	Sun *et al.*, 2010	↑	???	?	???	?	???	?
Atipamezole	Koskinen *et al.*, 2003	↑	???	?	???	?	???	?
Phenylephrine	???	?	???	?	???	?	Van Gaalen *et al.*, 2006b	–
Prazosin	Milstein *et al.*, 2010	–	???	?	???	?	???	?
Propranolol	Milstein *et al.*, 2010	–	???	?	???	?	???	?

↑: increase in impulsivity; ↓: decrease in impulsivity; –: no change in impulsivity. Pharmacological mechanisms of action of the drugs listed: atomoxetine: NA reuptake inhibitor; bupropion: DA-NA reuptake inhibitor; desipramine: NA-5-HT reuptake inhibitor; milnacipran: NA-5-HT reuptake inhibitor; guanfacine: α_2 agonist; clonidine: α_2 agonist; yohimbine: α_2 antagonist; atipamezole: α_2 antagonist; phenylephrine: α_1 agonist; prazosin: non-specific α antagonist used; propranolol: non-specific β antagonist.

into the DA system, there has been a growing resurgence of interest in the hypothesis that NA plays a key role in both the aetiology and treatment of this disorder (Biederman and Spencer, 1999; Biederman *et al.*, 2006; Arnsten *et al.*, 2007; Arnsten, 2009). The selective NA reuptake inhibitor atomoxetine (Strattera™) is currently one of the few non-stimulant medications found to be effective in treating ADHD (Spencer *et al.*, 2002b; Simpson and Perry, 2003), and the α_{2A} receptor agonist guanfacine has recently also been approved for treatment of this disorder (Connor and Rubin, 2010; Muir and Perry, 2010). Although bupropion, a DA-NA reuptake inhibitor, has also been suggested as a treatment for ADHD in subjects with co-morbid substance abuse (Conners *et al.*, 1996; Riggs *et al.*, 1998; Levin *et al.*, 2002), its efficacy at reducing ADHD symptoms appears lower than for other prescription drugs (Spencer *et al.*, 2002b). Similarly, desipramine can be efficacious at reducing impulsivity (as assessed broadly by the ADHD symptoms rating questionnaire) in ADHD populations (Wilens *et al.*, 1996; Spencer *et al.*, 2002a), but concerns over its safety in children may explain why it is not more widely prescribed (e.g. Riddle *et al.*, 1991; 1993; Amitai and Frischer, 2006).

Much of the work demonstrating that atomoxetine and guanfacine are effective in reducing the impulse control symptoms of ADHD did not use behavioural test batteries, but rather symptom ratings and questionnaires. There appears to be a relative paucity of data regarding the effects of these, and other, noradrenergic compounds in behavioural tests of impulsivity in human subjects. However, comparing the available human and rodent studies, there appears to be considerable overlap between the effects of acute atomoxetine on tests of motor impulsivity, with a number of reports showing improved impulse control of this kind (Chamberlain *et al.*, 2006; Blondeau and Dellu-Hagedorn, 2007; Robinson *et al.*, 2008; Navarra *et al.*, 2008b; Bari *et al.*, 2009; Barry *et al.*, 2009; Tsutsui-Kimura *et al.*, 2009). Desipramine also generally decreases motor impulsivity in both species, although this was observed in the SST in humans but the 5CSRT in rats (Singer *et al.*, 1995; Overtoom *et al.*, 2003; van Gaalen *et al.*, 2006a). Further cross-species similarity is observed concerning the effects of the α_2 receptor antagonist yohimbine which increased premature responding in both humans and rats (Swann *et al.*, 2005; Sun *et al.*, 2010), and a similar effect was observed on the 5CSRT following administration of atipamezole which has a similar mechanism of action (Koskinen *et al.*, 2003). Furthermore, guanfacine decreases premature responding in both the CPT (humans) (Chappell *et al.*, 1995; Scahill *et al.*, 2001) and 5CSRT (rats) (Milstein *et al.*, 2007). However, null effects were reported on the SST in humans after guanfacine administration (Muller *et al.*, 2005) while an increase in this form of impulsivity has been reported in the rodent model (Bari *et al.*, 2009).

Despite the fact that clonidine shares a primary pharmacological mechanism with guanfacine, in that they are both α_2 agonists, clonidine has a less selective receptor-binding profile for the α_{2A} receptor and is less favoured in the treatment of ADHD symptoms due to the significant vasodilation and reductions in blood pressure that can result (Daviss *et al.*, 2008; Spencer, 2009). It has also been suggested that the behavioural improvements observed likely reflect more of a sedative than anti-impulsivity action (Biederman and Spencer, 1999; Palumbo *et al.*, 2008). Repeated administra-

tion of clonidine did not improve go/no-go performance in ADHD children (van der Meere *et al.*, 1999). Only one study has reported the effects of acute clonidine on a test of impulsivity (delay discounting) in rats, and the drug increased rather than decreased impulsive choice (van Gaalen *et al.*, 2006b). The behavioural data largely match the clinical findings therefore that clonidine does not decrease any form of impulsivity (Singer *et al.*, 1995).

To summarize, the effects of noradrenergic compounds on impulsivity across humans and rats are largely consistent, particularly with regards to the CPT/5CSRT. Atomoxetine and desipramine decrease motor impulsivity in both species, whereas yohimbine has the opposite effect and clonidine produces little change. The fact that guanfacine increased SSRT in rats is surprising, and is the only really inconsistent observation, but this effect was only observed at the highest dose tested and may therefore indicate drug activity at non-α_2 receptors. The behavioural outcome at this higher dose may also reflect motor slowing or sedation rather than any specific effect on motor impulsivity.

The 5-HT system

The hypothesis that low 5-HT levels contribute to deficits in impulse control originated in the 1980s, following observations that decreased levels of circulating 5-HT metabolites dissociated impulsive from non-impulsive aggression in people (Linnoila *et al.*, 1983), and that chronically inhibiting the 5-HT system led to behavioural disinhibition in animals (Soubrie, 1986). Central 5-HT levels can be transiently reduced by depleting an individual's diet of the amino acid tryptophan, an essential precursor of 5-HT. Although tryptophan depletion has recently been shown to increase delay discounting in healthy volunteers (Schweighofer *et al.*, 2008), other studies have not observed any such change in impulsive choice (Crean *et al.*, 2002). Tryptophan depletion has been found to increase motor impulsivity in healthy subjects with a family history of alcoholism, as indicated by increases in SSRT and commission errors on the go/no-go task (LeMarquand *et al.*, 1999; Crean *et al.*, 2002). Increased impulsivity on the CPT has also been observed in male control subjects (Walderhaug *et al.*, 2002; 2008), while female subjects showed a greater decrease in mood (as assessed by the Profile of Mood States questionnaire) rather than elevated impulsivity (Walderhaug *et al.*, 2007). The ability of tryptophan depletion to increase this form of motor impulsivity is also enhanced by the short allele of the 5-HT transporter (Walderhaug *et al.*, 2010). In contrast, neither tryptophan depletion nor the 5-HT transporter polymorphism has been shown to affect the SSRT in healthy volunteers (Clark *et al.*, 2005). Hence, there are clearly a number of factors that determine whether low 5-HT will induce impulsive responding in a given individual, including the type of behavioural test used, as well as gender, family history and genotype. The overwhelming conclusion from reviewing the literature, though, is that low 5-HT can contribute to increased impulsivity across domains.

A similar pattern of data is observed regarding the effects of global reductions in 5-HT in the different rodent paradigms. Lesions to the 5-HT system significantly increase premature responding on the 5CSRT (Harrison *et al.*, 1997; Winstanley *et al.*, 2004), yet have null or mixed effects on the SST or delay-discounting task (Wogar *et al.*, 1993; Mobini *et al.*, 2000; Winstanley *et al.*, 2003b; 2005; Eagle *et al.*, 2009). However, administration of a 5-HT_{1A} receptor agonist, which leads to a temporary reduction in 5-HT efflux throughout the brain via its actions at pre-synaptic autoreceptors while also activating inhibitory 5-HT_{1A} receptors located post-synaptically (Bonvento *et al.*, 1992; Sharp *et al.*, 1996), has been found to increase impulsive choice on the delay-discounting task and premature responding on the 5CSRT (Table 3B) (Carli and Samanin, 2000; Winstanley *et al.*, 2005; van den Bergh *et al.*, 2006; Stanis *et al.*, 2008).

From a pharmacological perspective, the most widely used therapeutic drugs which act on the 5-HT system are the serotonin selective reuptake inhibitors (SSRIs). Although primarily used as antidepressants, this class of drug is now widely prescribed for a variety of psychiatric disorders including anxiety and obsessive–compulsive disorder (OCD) (Goddard *et al.*, 2008; Katzman, 2009), yet despite the association between low levels of 5-HT within the central nervous system and aspects of impulsivity, serotonergic medication is not routinely prescribed for ADHD. Indeed, the serotonergic contribution to ADHD is currently thought to be minimal, although amphetamine's actions on the 5-HT system may contribute to its 'paradoxical' calming effect in ADHD (Gainetdinov *et al.*, 1999). SSRIs are sometimes used in the treatment of PG, but clinical trials have provided equivocal results regarding their utility in this regard (see Williams *et al.*, 2008 for discussion). SSRIs have also been prescribed to those with BPD, but there is again some debate as to their efficacy, with the most robust improvements observed in the depressive rather than the impulsive symptoms (Binks *et al.*, 2006; Nose *et al.*, 2006; Herpertz *et al.*, 2007; Saunders and Silk, 2009). Hence, despite the substantial body of evidence to indicate that 5-HT is important for impulse control, this has not translated into efficacious pharmacological treatment for ICDs. This observation fits with the fact that, regarding the effects of acute administration of serotonergic drugs, no significant effects have been reported on any behavioural test of impulsivity in healthy volunteers (Table 3A) (Hart *et al.*, 1991; Del-Ben *et al.*, 2005; Chamberlain *et al.*, 2006; 2007; Wingen *et al.*, 2007; Iwamoto *et al.*, 2008; Overtoom *et al.*, 2009; Almeida *et al.*, 2010; Drueke *et al.*, 2010; Vollm *et al.*, 2010). Likewise, no changes were observed after 7 days of SSRI administration (Drueke *et al.*, 2010).

Preclinical data suggest that the disparity between these null findings and the seemingly strong association between reduced 5-HT function and high impulsivity relates to the heterogeneous nature of the serotonergic system. There are a multitude (14+) of distinct 5-HT receptors, which vary in both their location (pre- vs. post-synaptic, terminals vs. soma, distal vs. proximal dendrites) and their ability to either excite or inhibit the cell on which they are expressed (Barnes and Sharp, 1999; Bockaert *et al.*, 2006). Drugs which act as selective agonists or antagonists at a particular receptor subtype can therefore have very different effects on brain and behaviour. However, most research on human subjects has used drugs which do not differentiate between receptor subtypes, such as SSRIs, and these drugs likewise have no effect in the animal models (see Table 3B) (Evenden and Ryan, 1996;

Table 3A

The effects of acute administration of serotonergic compounds on different tests of impulsivity in humans

Drug	CPT Study	↑ – ↓	SST Study	↑ – ↓	Go/no-go Study	↑ – ↓	Delay discounting Study	↑ – ↓
Citalopram	Almeida *et al.*, 2010	–	Chamberlain *et al.*, 2006 Drueke *et al.*, 2010 Wingen *et al.*, 2007	–	Del-Ben *et al.*, 2005	–	???	?
Paroxetine	Iwamoto *et al.*, 2008	–	Overtoom *et al.*, 2009	–	???	?	???	?
mCPP	???	?	???	?	Vollm *et al.*, 2010	–	???	?
Buspirone	Hart *et al.*, 1991	–	Chamberlain *et al.*, 2007	–	???	?	???	?

↑: increase in impulsivity; ↓: decrease in impulsivity; –: no change in impulsivity. Pharmacological mechanisms of action of the drugs listed: citalopram: serotonin-selective reuptake inhibitor (SSRI); paroxetine: SSRI; mCPP: non-selective 5-HT_{2C} agonist; buspirone is 5-HT_{1A} partial agonist.

Table 3B

The effects of acute administration of serotonergic compounds on different tests of impulsivity in rats

Drug	5CSRT Study	↑ – ↓	SST Study	↑ – ↓	Go/no-go Study	↑ – ↓	Delay discounting Study	↑ – ↓
Citalopram	???	?	Bari *et al.*, 2009	–	???	?	Evenden and Ryan, 1996	–
Fluvoxamine	Tsutsui-Kimura *et al.*, 2009	–	???	?	???	?	???	?
5-HT_{1A} agonist	Carli and Samanin, 2000[a] Winstanley *et al.*, 2003a[a]	↑ –	???	?	???	?	Winstanley *et al.*, 2005[a] Stanis *et al.*, 2008 van den Bergh *et al.*, 2006[b]	↑
5-HT_{1A} antagonist	Winstanley *et al.*, 2003a Milstein *et al.*, 2010	–	???	?	???	?	Winstanley *et al.*, 2005	–
5-$HT_{1A/1B}$ agonist	???	?	???	?	???	?	van den Bergh *et al.*, 2006	↓
5-HT_{1B} antagonist	Milstein *et al.*, 2010	–	???	?	???	?	van den Bergh *et al.*, 2006	–
5-HT_{2A} antagonist	Higgins *et al.*, 2003 Winstanley *et al.*, 2003a Winstanley *et al.*, 2004 Fletcher *et al.*, 2007	↓	???	?	???	?	???	?
5-HT_{2C} agonist	Navarra *et al.*, 2008a	↓	???	?	???	?	???	?
5-HT_{2C} antagonist	Higgins *et al.*, 2001 Winstanley *et al.*, 2004 Fletcher *et al.*, 2007	↑	???	?	???	?	???	?
5-$HT_{2A/2C}$ agonist	Koskinen *et al.*, 2000 Koskinen and Sirvio, 2001	↑	???	?	???	?	???	?
5-$HT_{2A/2C}$ antagonist	Ruotsalainen *et al.*, 1997[c] Passetti *et al.*, 2003[d] Talpos *et al.*, 2006[d] Fletcher *et al.*, 2007[d]	↓	???	?	???	?	Talpos *et al.*, 2006[d]	–
5-$HT_{2B/C}$ antagonist	Talpos *et al.*, 2006	–	???	?	???	?	Talpos *et al.*, 2006	↓
5-HT_6 antagonist	Talpos *et al.*, 2006	–	???	?	???	?	Talpos *et al.*, 2006	–

↑: increase in impulsivity; ↓: decrease in impulsivity; –: no change in impulsivity. Pharmacological mechanisms of action of the drugs listed: citalopram: serotonin-selective reuptake inhibitor (SSRI); fluvoxamine: SSRI. Drugs used: 5-HT_{1A} agonist: 8-OH-DPAT[a], flesinoxan[b]; 5-HT_{1A} antagonist: WAY100635; 5-$HT_{1A/B}$ agonist: eltoprazine; 5-HT_{1B} antagonist: GR127935; 5-HT_{2A} antagonist: M100907; 5-HT_{2C} agonist: WAY-163909; 5-HT_{2C} antagonist: SB242,084; 5-$HT_{2A/2C}$ agonist: DOI; 5-$HT_{2A/2C}$ antagonist: ritanserin[c], ketanserin[d]; 5-$HT_{2B/C}$ antagonist: SER-082; 5-HT_6 antagonist: SB-270146-A.

Bari *et al.*, 2009; Tsutsui-Kimura *et al.*, 2009). As such, the potential utility of drugs which target branches of the 5-HT system may have been overlooked, or at least, any data to indicate progress to the contrary is not yet in the public domain. The majority of preclinical studies have been conducted using the 5CSRT, in which a remarkably consistent pattern of results has emerged concerning the opposing action of 5-HT_{2A} and 5-HT_{2C} receptors: both a 5-HT_{2A} antagonist and 5-HT_{2C} agonist decrease premature responding, whereas a 5-HT_{2C} antagonist increases this form of impulsivity (Higgins *et al.*, 2001; 2003; Winstanley *et al.*, 2003a; 2004; Fletcher *et al.*, 2007; Navarra *et al.*, 2008a). Interestingly, agents with mixed selectivity for the 5-HT_{2A} and 5-HT_{2C} receptors tend to resemble 5-HT_{2A} selective agents in terms of their effects on the 5CSRT (Ruotsalainen *et al.*, 1997; Koskinen *et al.*, 2000; Koskinen and Sirvio, 2001; Passetti *et al.*, 2003; Talpos *et al.*, 2006; Fletcher *et al.*, 2007). Although a 5-$HT_{2A/2C}$ antagonist had no effects on the delay-discounting paradigm (Talpos *et al.*, 2006), highly selective ligands have yet to be tested on this and other forms of impulse control, and clearly selectivity may be important given the opposing action of the receptors.

In terms of the utility of these observations, there is continuing interest in the role of 5-HT and aspects of impulsivity with respect to substance abuse. In addition to decreasing motor impulsivity, the 5-HT_{2A} antagonist M100907 has been found to decrease reinstatement of cocaine-seeking, an animal model of relapse to addiction (Fletcher *et al.*, 2002; Nic Dhonnchadha *et al.*, 2009). A similar reduction in drug reinstatement has been observed following administration of selective 5-HT_{2C} agonists (Burbassi and Cervo, 2008; Fletcher *et al.*, 2008b), likely through their actions in the mPFC (Pentkowski *et al.*, 2010). High levels of impulsivity on both the 5CSRT and delay-discounting tasks have been reported following withdrawal from cocaine self-administration (Winstanley *et al.*, 2009; Mendez *et al.*, 2010). Given the observation previously noted that high impulsivity appears to contribute to treatment failure in cocaine addiction, 5-HT_{2A} antagonists/5-HT_{2C} agonists may be of benefit in this regard, and may likewise be of use in the treatment of nicotine dependence (Fletcher *et al.*, 2008a).

Future directions: behavioural models of decision-making under risk or uncertainty

While there is little doubt that the delay-discounting model has been the most successful and widely adopted assessment of impulsive decision-making, there is increasing interest in evaluating judgements made when outcomes are uncertain or probabilistic, and how that relates to the broad construct of impulsivity. The Iowa Gambling Task (IGT) was developed in the 1990s to model 'real-life' decision-making under risk and uncertainty (Bechara *et al.*, 1994), and is probably the most widely used test of its kind. In this paradigm, subjects are required to pick between options (decks of cards) associated with varying levels and probabilities of wins and losses in order to win money or points. The optimal strategy is to choose from 'safer', or more advantageous, decks which yield smaller immediate rewards but also deliver lower penalties, hence leading to greater net gain. A preference for the disadvantageous 'high-risk, high-reward' decks is maladaptive in this task in that the subject accrues less money in the course of the session, and as such may tap into non-planning impulsivity. Indeed, poor choice on the IGT has been described previously as impulsive (e.g. Verdejo-Garcia *et al.*, 2007b).

However, current data suggest that choice between immediate and delayed rewards does not co-vary with sensitivity to probabilistic or risky rewards (Holt *et al.*, 2003; Lamm *et al.*, 2006). Clinical populations in which both choice and motor impulsivity is high tend to perform poorly on the IGT, as demonstrated by the increased preference for the disadvantageous decks in substance abusers (Bechara *et al.*, 2001; 2002; Verdejo-Garcia *et al.*, 2007a), pathological gamblers (Goudriaan *et al.*, 2005), BPD patients (Haaland and Landro, 2007) and subjects experiencing acute mania (Adida *et al.*, 2008). However, deficits on this task are also observed in psychiatric disorders in which deficits in impulse control are not a key symptom, such as schizophrenia (Shurman *et al.*, 2005; Yip *et al.*, 2009). Furthermore, the poor IGT score observed in cocaine abusers and pathological gamblers does not correlate with any aspects of impulsivity as assessed by the BIS-11, unlike the number of commission errors made on the CPT (Petry, 2001; Kjome *et al.*, 2010).

Hence, despite the fact that highly impulsive individuals tend to perform more poorly on the IGT, decision-making under risk or uncertainty likely reflects a dissociable psychological construct. There are also other tests of risky decision-making, such as the Balloon Analogue Risk Task (BART), which likewise indicate that risk-taking is synergistic with, but dissociable from, trait impulsivity (Lejuez *et al.*, 2003; Hunt *et al.*, 2005; Fernie *et al.*, 2010). Interestingly, scores on the IGT and BART again do not correlate, further indicating that risk-seeking, like impulsivity, may be multifaceted in nature (Lejuez *et al.*, 2003). It is worth noting that animal models of both the IGT (van den Bos *et al.*, 2006; Rivalan *et al.*, 2009; Zeeb *et al.*, 2009) and BART (Jentsch *et al.*, 2010) have been developed. Characterization of the neural and neurochemical influences controlling these complex choice tasks will no doubt be beneficial in determining their relationship with different forms of impulsivity, and their potential utility in drug development for disorders in which such decision-making is compromised.

Future directions: novel pharmacological targets

While the current medications used to treat ICDs are very effective for some individuals, others do not obtain the same benefits. The use of stimulant drugs to treat ADHD can be problematic, either from the perspective that parents are unhappy about giving stimulant drugs to children, or in terms of their abuse potential in adults. Such drugs will also never be appropriate for treating impulse control symptoms in either substance abusers or those with BD. The glutamate system has been the subject of more intensive research as a viable target for psychiatric compounds, largely with respect to schizophrenia and Alzheimer's, but also as agents to reme-

diate substance abuse (Dackis and O'Brien, 2003; Bowers *et al.*, 2010). Glutamate is the major excitatory neurotransmitter in the brain, and its ubiquitous nature made it at first an unlikely target for pharmacotherapies. However, as more is discovered regarding the subunit structure of glutamatergic receptors, and how the distribution of such subunits can vary between different brain regions and neuronal cell types, there is increasing hope that glutamatergic neurotransmission can be modified directly in a way that will remedy aberrant signalling yet leave normal glutamatergic transmission unimpaired. Ampakines are positive allosteric modulators (PAMs) of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors which may have therapeutic efficacy for ICDs and other CNS disorders (Lynch, 2006; Lynch and Gall, 2006). Rather than acting as direct agonists at metabotropic glutamate receptors (mGluRs), such compounds can improve the efficiency of regular glutamatergic signalling, and may therefore be capable of remedying hypofunction without the risk of overstimulation. Ampakines (CX516 & CX546) can reduce the hyperactivity observed in DAT knockout mice (Gainetdinov *et al.*, 2001), potentially indicating they could be useful in ADHD or BD, but their effects on impulsivity are unknown.

mGluR PAMs may also be promising compounds in this regard. ADX47273, a mGluR5 PAM, has been suggested as a pro-cognitive agent, and a decrease in premature responding on the 5CSRT has been reported following its administration (Liu *et al.*, 2008). However, premature responding appears to be unusually high in the cohort of rats tested, probably because these impulsive responses were not actually punished in the version of the task, thus making it difficult to judge the true size of a particular effect. Nevertheless, this is a promising outcome. Mice lacking mGluR5 receptors neither self-administer cocaine nor exhibit cocaine-induced hyperactivity, effects which are paralleled by the selective mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine (MPEP) (Chiamulera *et al.*, 2001; McGeehan *et al.*, 2004). Furthermore, an increase in mGluR5 mRNA has been reported in the orbitofrontal cortex of rats with a history of cocaine self-administration (Winstanley *et al.*, 2007). Given that mGluR5 receptors increase GABA-mediated inhibition through excitation of inhibitory interneurons (Chu and Hablitz, 1998), receptor up-regulation may contribute to the decreased activity of this brain region thought to contribute to impulse control deficits in cocaine abusers (Volkow and Fowler, 2000; Winstanley, 2007). Based on these findings, mGluR5 PAMs like ADX47273 may well be efficacious in treating impulsivity in general, and drug-users in particular. The current data also suggest that motor impulsivity models such as the 5CSRT would provide a good screen for these compounds. However, despite the considerable evidence suggesting that high motor and choice impulsivity is one of the key determinants of poor treatment outcome and a major contributor to the negative cycle of addiction, it is unclear whether these behavioural symptoms will ever be a priority of either pharmaceutical companies or health practitioners.

Another putatively pro-cognitive drug, modafinil, has also been found to reduce premature responding in rats on a task similar in design to the 5CSRT (Morgan *et al.*, 2007; but see Waters *et al.*, 2005 for conflicting data). The exact mechanism of action of this compound remains to be determined, but it has been suggested to act by inhibiting GABA release, potentiating activity in the DA system (although to a much lesser degree than amphetamine or cocaine), activating the glutamate and orexin systems as well as acting as a noradrenergic α_1 agonist (Cox and Pappagallo, 2001; Ballon and Feifel, 2006). Acute administration of modafinil also improves performance of the SST in both healthy volunteers (Turner *et al.*, 2003) and ADHD patients (Turner *et al.*, 2004). Furthermore, modafinil decreased the drive to play slot machines in PG subjects and improved IGT performance, but only if they were more impulsive on the SST; in less impulsive subjects, modafinil had the opposite effect (Zack and Poulos, 2008). Whether this drug will be approved for treatment of ICDs is currently unclear, yet its use has been advocated in both cocaine dependency (Dackis and O'Brien, 2003; Martinez-Raga *et al.*, 2008) and ADHD (Biederman *et al.*, 2005; Boellner *et al.*, 2006).

Given that modafinil also promotes alertness and wakefulness, and that these properties of the drug may directly contribute to its effects on motor impulsivity, compounds which target the orexin system may also show promise in this regard (Swanson, 2003), although this remains highly speculative. Similarly, considering the overlap between impulsivity and addiction, drugs which target the opioid and cannabinoid system may have effects on impulse control (see Pattij and Vanderschuren, 2008 for details).

Final summary and discussion

Overall, there is a fair degree of consistency regarding the effects of drugs on rodent and human tests of impulsivity. However, the field could benefit from more systematic comparisons of drug effects across different tests of impulsive behaviour, in rats if not practical in humans. Unfortunately, there are currently insufficient data to determine whether the outcome of pharmacological manipulations of go/no-go performance translate accurately between species. Interestingly, the predictive validity of the other rat models varies in terms of the class of drugs in question. For example, results from the 5CSRT match those from the CPT when considering noradrenergic agents, whereas the SST and delay-discounting task produce better cross-species translation regarding the psychostimulant drugs. Regarding the serotonergic system, considerably more preclinical data is available regarding the effects of selective 5-HT compounds, but to the extent that SSRIs do not affect measures of impulse control in humans or rats, there is remarkable concordance. It should be noted that, given the time course of the antidepressant effects of this class of drugs, a beneficial effect of SSRIs on impulsive behaviour may be observed after chronic administration for longer time periods than have been evaluated to date, and this remains to be empirically determined.

It would no doubt be useful at this point if one were able to make a general recommendation as to which task should be used at which stage of drug development for which class of compounds. Table 4 attempts to summarize all the relative advantages and disadvantages of the different behavioural models discussed, both in terms of the validity of the different tasks as well as training complexity and other logistics. Regarding the number of sessions required before a stable

Table 4

Summary table comparing the different behavioural tests of impulsivity using multiple factors

Factor	5CSRT	SST	Go/no-go	Delay discounting
Frequency of use in pharmacological experiments	Very high	Intermediate	Low	High
Training sessions to baseline	~45–55	~45–55	~30–35	~35–40
Session duration	30 min	20 min	40 min	60–100 min
Data currently available in mice?	Y	N	Y	Y
Measures multiple cognitive processes	Y	N	N	N
Level of inter-individual variation	Intermediate	Low (if task parameters set appropriately)	Low[1]	High
Ease of training:	Intermediate:	More complex:	Easy:	Easy:
Task parameters must be individually titrated for each rat during (a) training (b) testing	(a) Y (b) N	(a) Y (b) Y	(a) N (b) N	(a) N (b) N
Face validity	Intermediate	Very high	Very high	High
Construct validity	High	Very high	Very high	Intermediate
Predictive validity (from a translational pharmacology perspective)	Intermediate	High	Insufficient data	High

[1]This is partly assumed from the lack of reports in the literature of baseline differences in performance influencing outcome manipulation.

baseline is established, it is clear that none of these paradigms is ideal for high-throughput screening as they simply take too long to train. Outside of academic research, it therefore appears unlikely that these methods would be useful for target identification. However, once a compound has been flagged as being potentially useful in the treatment of high impulsivity (e.g. using *in vitro* screens, receptor binding profiles, *in vivo* imaging data, or even through indications in the academic literature), then investigating its effects on one or more behavioural assays could prove fruitful prior to engaging in a clinical proof-of-concept study.

As it is currently unclear as to which dimension of impulsivity is more or less important for any particular clinical condition, which task to use will depend on a number of variables, including whether the compound has a similar mechanism to others already identified (see paragraph above). Another important consideration concerns the level of experience a particular group has with behavioural testing of this kind, as the degree of complexity involved in implementing the training differs from task to task (e.g. the training regimen for delay-discounting task is relatively simple compared to the SST). If the compound has a very novel or unknown mechanism of action, the 5CSRT is likely a good choice as it has been incredibly well characterized, and provides a measure of attention as well as motor impulsivity. Furthermore, no drug which affects motor impulsivity in humans has so far failed to alter premature responding in the 5CSRT, even if the direction of the effects can be opposing.

Conclusion

In summary, given the degree of translation outlined here, it would appear that there is some untapped potential in terms of using the rodent models of different aspects of impulsivity for drug discovery, both for target validation and to support proof-of-concept studies. Regarding the adoption of noradrenergic drugs to treat ADHD, behavioural pharmacology in non-human subjects was critical in demonstrating the importance of NA within the mPFC in terms of optimizing cognitive behaviours such as working memory and attention (Arnsten *et al.*, 2007; Arnsten, 2009). Although data from impulsivity models strongly supports the use of atomoxetine to treat high levels of impulsivity, these data appeared to follow rather than lead the push for drug development. This likely reflects the relatively recent shift in focus to the NA system within the impulsivity field, but the data indicate that positive findings in these rodent behavioural tests can be predictive of clinical benefit. As such, the fact that multiple studies have observed consistent improvements in motor impulsivity with 5-HT_{2A} antagonism/5-HT_{2C} agonism may warrant further investigation from a therapeutics perspective, particularly as the stimulant drugs which are used so successfully in ADHD treatment may not be appropriate for some highly impulsive populations, such as those with acute mania, substance abuse or problem gambling. Drugs which do not target the monoamine system, such as PAMs, may also be useful in this regard. Given that impulsivity is a core component of a number of disorders which are hard to model and can be problematic to treat, appropriate use of animals models to evaluate putative pharmacotherapies could enable real progress in the search for better drug treatments for ICDs.

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Conflict of interest

CAW has previously consulted for Theravance.

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