

Highly impulsive rats: modelling an endophenotype to determine the neurobiological, genetic and environmental mechanisms of addiction

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Impulsivity describes the tendency of an individual to act prematurely without foresight and is associated with a number of neuropsychiatric co-morbidities, including drug addiction. As such, there is increasing interest in the neurobiological mechanisms of impulsivity, as well as the genetic and environmental influences that govern the expression of this behaviour. Tests used on rodent models of impulsivity share strong parallels with tasks used to assess this trait in humans, and studies in both suggest a crucial role of monoaminergic corticostriatal systems in the expression of this behavioural trait. Furthermore, rodent models have enabled investigation of the causal relationship between drug abuse and impulsivity. Here, we review the use of rodent models of impulsivity for investigating the mechanisms involved in this trait, and how these mechanisms could contribute to the pathogenesis of addiction.

Defining impulsivity: a human trait

Impulsivity is typically classified as a predisposition for premature, poorly planned, unduly risky or inappropriate actions (Daruma and Barnes, 1993). This behavioural construct consists of a heterogeneous repertoire of factors, each with independent but potentially overlapping neurobiological substrates (Evenden, 1999). Impulsivity in its simplest form consists of at least two major components: motor disinhibition (impulsive action) and impulsive decision-making (impulsive choice). Theorists, however, suggest that impulsivity encompasses a more complex array of behavioural processes, including urgency, risk-taking, sensation-seeking, non-planning, lack of premeditation, a disregard for future consequences and insensitivity to punishment (Barratt, 1985; Evenden, 1999; Moeller et al., 2001; Monterosso and Ainslie, 1999; Whiteside and Lynam, 2003).

Although still a matter of considerable debate, impulsivity has been postulated to originate from complex, dynamic ecological variables. In this sense, impulsivity might offer a biological advantage in certain social or environmental settings (Williams and Taylor, 2006) and, as such, 'functional' impulsivity favours advantageous outcomes and indeed is an important aspect of human behaviour without which individuals would fail to take acceptable risks or pursue unexpected opportunities. In contrast,

'maladaptive' impulsivity is akin to the largely accepted definition of impulsivity as excessively risky, premature and inappropriate actions associated with negative outcomes. Maladaptive impulsivity has been shown to predict antisocial behaviour, unlike functional indices of impulsivity, which facilitate extraversion and sociability (Cale and Lilienfeld, 2006). Indeed, in its extreme form, maladaptive impulsivity has been associated with a wide range of neuropsychiatric morbidities, including personality (Perry and Körner, 2011) and mood (Lombardo et al., 2012) disorder, drug abuse and addiction (Ersche et al., 2010), suicide (Dougherty et al., 2004), and attention deficit hyperactivity disorder (ADHD) (Avila et al., 2004).

The diverse taxonomies of impulsivity have led to the development of a variety of self-report questionnaires evaluating these factors [e.g. Eysenck personality questionnaire (Eysenck and Eysenck, 1984), Barratt (Barratt, 1985), UPPS (Whiteside and Lynam, 2003) and Dickman Impulsiveness Scales (Monterosso and Ainslie, 1999)]. There are, however, a number of inherent limitations associated with self-report measures (Wilson and Dunn, 2004), which can be exacerbated in impulsive individuals, who might lack introspection and the ability to appropriately perceive their behaviour. Indeed, it has been suggested that questionnaire-based methods have contributed to the heterogeneity of findings relating to the biological basis of impulsivity (Eisenberg et al., 2007). Computer-based clinical psychometric behavioural tests, which subjectively assess aspects of impulsive choice or impulsive action, provide a more objective measure of impulsivity (reviewed by Chamberlain and Sahakian, 2007; Kertzman et al., 2006). Among these tests, delay-discounting is the most commonly employed measure of impulsive choice and involves individuals making a series of choices between small, immediate rewards versus larger rewards received after a longer delay. Impulsive individuals prefer immediate rewards even if they are smaller than those offered at a later period of time (Richards et al., 1999). The go/no-go task is used to assess deficits in response initiation/inhibition (impulsive

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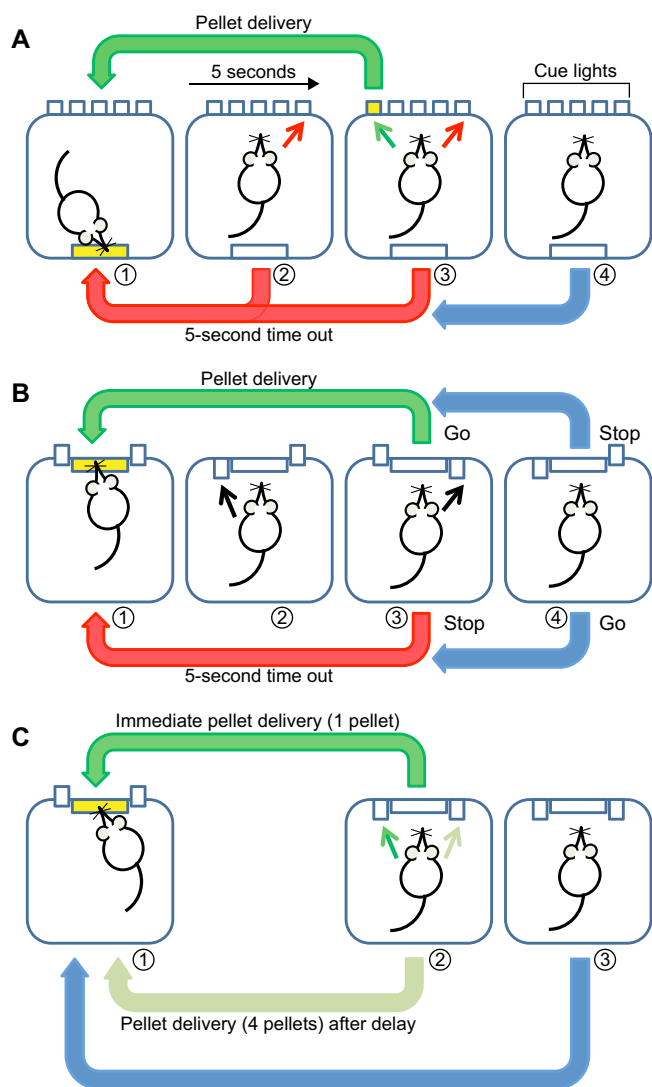


Fig. 1. Schematic representation of operant-based tests of impulsivity in rodents. Green arrows represent correct responses and outcomes, whereas red arrows denote incorrect responses and associated outcomes. Blue arrows denote outcomes associated following an omitted response. Adapted with permission from Dalley and Roiser (Dalley and Roiser, 2012). (A) The five-choice serial reaction time task (5CSRTT) requires animals to wait for a food-predictive light cue before carrying out the response. The trial is initiated when the animal enters the illuminated food magazine (panel 1) and, following a delay (5 seconds), one of five cue lights is briefly illuminated (panel 3). If subjects nose-poke in the corresponding aperture, they receive a food reward (green arrow, panel 3). Responses that are made prior to the presentation of the cue light (impulsive responses; panel 2), are incorrect (red arrow, panel 3) or are withheld (panel 4) are punished by a 5-second time out during which the house light is extinguished. (B) The stop-signal reaction time task requires subjects to withhold reinforced responding following presentation of a tone cue (stop signal). The task begins following entry into the food magazine (panel 1), after which the left lever is introduced into the arena (panel 2). Responding on this lever introduces the right 'reward' lever, which, if depressed during a go trial (no tone), results in delivery of a food reward (panel 3). During a stop trial (during which a tone is presented), responding on the right lever is punished by a time out. If no responses are made during a stop trial, a food reward is delivered (panel 4). Conversely, if no response is made during a go trial, this is punished by a time-out period. Impulsive individuals have difficulty inhibiting responses during stop trials. (C) The delay-discounting task requires subjects to choose between a small immediate food reward or a larger reward delivered following a delay. The task begins following entry into the food magazine (panel 1), after which animals are presented with two levers (panel 2): one provides a small immediate food reward (left lever) and the other a larger reward following a delay (right lever). Omitted responses (panel 3) are unrewarded. Impulsive individuals prefer the immediate over the delayed reward.

action). This test requires subjects to perform a binary-choice reaction time task where they respond to one stimulus (e.g. a plain square) and must inhibit a response to a second stimulus (e.g. a patterned square). Impulsive individuals tend to make more rapid, but incorrect, responses during this task (Riccio et al., 2002). In the stop-signal reaction time task, which is also used to assess impulsive action, subjects perform a primary visual binary-choice reaction time task and, on a portion of trials, are instructed to inhibit that response upon the presentation of a stop signal (e.g. an auditory or visual stimulus), which can occur at any time at or after the onset of the primary stimulus. Impulsive individuals show a higher rate of failure to inhibit responses following presentation of the stop signal (Logan et al., 1997).

Importantly for the investigation of the biological basis of impulsivity, indices of impulsive behaviour in humans have analogues in animal behaviour. Delay-discounting, go/no-go and stop-signal tasks have all been translated to operant-based paradigms and have been used to assess impulsivity in rodents (reviewed by Winstanley, 2011). Other operant-based methods, particularly the five-choice serial reaction time task (5CSRTT) (Fig.

1), which assays impulsive action based on premature responses for a food-predictive, brief light stimulus (Robbins, 2002), are also widely used. In this Review, we discuss the use of rodent models of impulsivity, particularly in relation to the endogenous expression of impulsive behaviour (referred to here as trait or trait-like impulsivity), for investigating the underlying mechanisms of this behaviour and its potential aetiological relationship as an endophenotype of the pathogenesis of addiction.

Neurobiology of impulsivity

Clinical studies investigating the neuroanatomical and psychopharmacological substrates of impulsivity have largely implicated monoaminergic corticostriatal systems. Brain imaging studies in humans have identified structural and functional alterations in distinct regions of the prefrontal cortex (PFC) (Wilbertz et al., 2012) and associated corticostriatal circuitry (Carmona et al., 2009) in impulsive individuals. It has been suggested that dysfunctional monoaminergic signalling, particularly related to dopaminergic and noradrenergic function, contribute to impulsivity based on the therapeutic efficacy of drugs used to treat ADHD, such as the mixed dopamine (DA)/noradrenaline reuptake inhibitor methylphenidate and the noradrenaline reuptake inhibitor atomoxetine (Del Campo et al., 2011). Indeed, positron emission tomography studies have identified alterations in DA release (Buckholtz et al., 2010; Oswald et al., 2007) and the availability of DA receptors D2 and/or D3 (referred to here as D2-like receptors) in the striatum (Ghahremani et al., 2012; Lee et al., 2009) of impulsive individuals. Serotonergic (5HT) dysfunction has also

been implicated, with enhanced levels of impulsivity predictive for reduced 5HT2A receptor and 5HT transporter binding in the PFC (Lindström et al., 2004; Meyer et al., 2008).

Investigations of the heritability of impulsivity have also identified polymorphisms in genes involved in monoaminergic function, including those encoding the DA transporter (Congdon et al., 2008), the 5HT2A (Reist et al., 2004) and 5HT2B (Bevilacqua et al., 2010) receptors, and the monoamine oxidase A enzyme (Liu et al., 2011). However, there is also increasing evidence for environmental risk factors in impulsivity, particularly relating to the expression of genetic vulnerability for impulsivity (Bezdjian et al., 2011). For example, a polymorphism in the DA D4 receptor was only found to be associated with impulsivity in individuals who were exposed to low socioeconomic status during childhood (Sweitzer et al., 2012).

Clinical investigations into the biological basis of impulsive behaviour are often confounded by co-expression of disease-specific symptoms. Although limited by anthropomorphism, animal models enable the relatively selective investigation of behavioural endophenotypes. Experimental approaches that evoke impulsive behaviour in animals, effected either pharmacologically or by selective brain lesions, have dissected the contribution of individual brain regions and transmitter systems to impulsive behaviour (Dalley and Roiser, 2012; Eagle and Baunez, 2010; Winstanley, 2011) (Tables 1, 2). These studies accord with findings in humans implicating the monoaminergic corticostriatal systems in impulsivity; however, there is additional evidence for an involvement of cannabinoid, opioid, glutamatergic and cholinergic signalling mechanisms in impulsive behaviour (Pattij and Vanderschuren, 2008). Furthermore, the contribution of each of these anatomical regions and transmitter systems varies between different impulsivity subtypes (Pattij and Vanderschuren, 2008).

Animal models of trait-like impulsivity

Ecologically valid animal models that capture the intrinsic qualities of impulsive behaviour arguably have greater face and construct validity than those generated using invasive approaches (e.g. brain lesions, administration of pharmacological agents). Studies that

modulate impulsivity using invasive approaches can be confounded by inadvertently investigating the effects associated with the particular manipulation, rather than the underlying neurobiology that is responsible for maladaptive impulsivity. Thus, animals that exhibit trait impulsivity have provided a useful experimental approach to the investigation of impulsivity. To date, a number of studies have identified particular strains of rodents that demonstrate increased levels of impulsivity (trait or trait-like impulsivity), including Roman high avoidance (RHA) rats (Moreno et al., 2010), spontaneously hypertensive rats (SHRs) (Adriani et al., 2003), and rats exhibiting naturally high impulsive behaviour on the 5CSRTT (Dalley et al., 2007) and delay-discounting task (Broos et al., 2012; Perry et al., 2005).

A limited number of studies have investigated the neurobiology of trait impulsivity in rodents; these have predominantly been carried out using animals displaying enhanced impulsive responding on the 5CSRTT. A diminished availability of D2-like receptors in the ventral striatum is observed in rats impulsive for the 5CSRTT (Dalley et al., 2007). Enhanced D1-receptor-mediated neurotransmission in the nucleus accumbens core (Ohno et al., 2012), and increased mRNA expression of this receptor in the PFC, has been shown to be predictive of delay-discounting impulsivity in SHRs (Loos et al., 2010). Pharmacological enhancement of DA signalling has been shown to increase impulsive responding, whereas administration of D2-like receptor agonists reduces impulsivity in rats exhibiting impulsive behaviour on the 5CSRTT (Fernando et al., 2012). These findings suggest that dopaminergic modulation of impulsivity can be receptor-subtype- and brain-region-dependent. For example, administration of the D2-like receptor antagonist nafadotride into the nucleus accumbens shell was found to enhance premature responding, whereas infusions into the core reduced premature responding in trait impulsive rats (Besson et al., 2010). There is also evidence for dysfunction in noradrenergic systems in trait impulsive animals: systemic administration of a noradrenaline reuptake inhibitor was found to reduce impulsivity, an effect potentially mediated by alpha 2A receptors (Fernando et al., 2012).

Table 1. Selected references for effects of anatomically localised brain lesions on impulsive responding in rats

Brain region affected	Effect on impulsive action (motor disinhibition)	Effect on impulsive choice (delay discounting)
Infralimbic cortex	↑ (Chudasama et al., 2003)	
Anterior cingulate cortex	↑ (Muir et al., 1996)	= (Cardinal et al., 2001)
	↑ (Eagle et al., 2008)	↓ (Winstanley et al., 2004a)
Orbitofrontal cortex	Lateral	↑ (Mar et al., 2011)
	Medial	↓ (Mar et al., 2011)
Dorsal striatum	↑ (Rogers et al., 2001)	
Nucleus accumbens	Core	↑ (Pothuizen et al., 2005)
	Shell	= (Pothuizen et al., 2005)
		↑ (Cheung and Cardinal, 2005)
Hippocampus	Dorsal	= (Abela et al., 2012)
	Ventral	↑ (Abela et al., 2012)
Basolateral amygdala		↑ (Winstanley et al., 2004a)
Subthalamic nucleus	↑ (Uslaner and Robinson, 2006)	↓ (Uslaner and Robinson, 2006)

↑ and ↓ denote an increase and decrease in impulsive responding, respectively; = denotes no effect. For a comprehensive review, see Eagle and Baunez, and Winstanley (Eagle and Baunez, 2010; Winstanley, 2011).

It is notable that, similar to ADHD (Sullivan et al., 2012), there is growing evidence for genetic influences in trait impulsivity in rodents. For example, there are reports demonstrating the stability of impulsive behaviour within, and variability between, inbred strains of mice (Gubner et al., 2010; Isles et al., 2004; Logue et al., 1998; Loos et al., 2009; Peña-Oliver et al., 2012), and a genome-wide association study in our own laboratory has found significant evidence of heritability of impulsivity in a multi-generational pedigree of outbred rats (S. Pitzoi, A. Mar, T. Robbins, E. Petretto, T. Aitman and J.W.D., unpublished findings). Moreover, studies using transgenic animals have provided persuasive evidence that genetic influences contribute to impulsivity (e.g. Peña-Oliver et al., 2012). Many of these studies aim to elucidate the contribution of genes and polymorphisms already identified as risk factors for impulsive behaviour in human studies [e.g. the serotonin transporter knockout rat (Homberg et al., 2007)]; however, previously unknown genetic mechanisms have also been identified, for example relating to genomic imprinting (Davies et al., 2005; Doe et al., 2009), that suggest a potential role for epigenetic mechanisms and gene-environment interactions in the expression of impulsivity.

Genetic studies in inbred mice have confirmed an environmental component and role for gene-environment interactions in the expression of impulsive behaviour (Isles et al., 2004; Loos et al., 2009). Factors such as rearing conditions [e.g. maternal separation, (Lovic et al., 2011)], prenatal or adolescent exposure to certain drugs such as alcohol (Bañuelos et al., 2012) and nicotine (Schneider et al., 2011), and environmental conditions [e.g. enrichment (Perry et al., 2008)], reportedly alter levels of impulsivity in rodents. The mechanisms through which environmental manipulations affect levels of impulsivity are still under investigation; however, plasticity mechanisms in dopaminergic function in corticostriatal circuitry are implicated in these phenomena. For example, both environmental enrichment and maternal separation alter levels and/or functioning of DA transporters in the corticostriatal system (Womersley et al., 2011; Zhu et al., 2005).

Trait-like impulsivity in rodents: a vulnerability marker of addiction

Animal models of trait impulsivity provide the opportunity to investigate the role of impulsivity in neuropsychiatric disorders such as addiction. Although the link between addiction and relapse vulnerability and impulsivity is well established in the clinical literature (reviewed by Verdejo-García et al., 2008), it has been difficult to dissect the causal effect of this relationship. Studies in rodents indicate that trait impulsivity is predictive of addiction-related behaviours, although this relationship is dependent on impulsivity sub-type and drug class (Belin et al., 2008; Dalley et al., 2007; Perry et al., 2005; Poulos et al., 1995). Both RHA (Moreno et al., 2010) and SHR (Harvey et al., 2011) lines display susceptibility to psychostimulants, whereas rats selected for trait action impulsivity show enhanced self-administration of cocaine (Dalley et al., 2007), nicotine (Diergaarde et al., 2008), alcohol (Radwanska and Kaczmarek, 2012) and methylphenidate (Marusich and Bardo, 2009), but not heroin (McNamara et al., 2010). Trait-like impulsive rats further show enhanced conditioned place preference to amphetamine (Yates et al., 2012), have a higher propensity to develop compulsive cocaine self-administration (Belin et al., 2008)

and show increased rates of 3,4-methylenedioxymethamphetamine (MDMA)-primed drug-seeking (Bird and Schenk, 2012) and cue-induced relapse for cocaine-seeking (Economidou et al., 2009). Furthermore, impulsive choice has been shown to predict increased alcohol (Oberlin and Grahame, 2009; Poulos et al., 1995) and nicotine (Diergaarde et al., 2008) consumption, as well as resistance to extinction and enhanced relapse propensity to both nicotine (Diergaarde et al., 2008) and cocaine (Broos et al., 2012). There is conflicting evidence, however, regarding the relationship of impulsive choice to cocaine and opiate consumption, with studies both supporting (Anker et al., 2009; García-Lecumberri et al., 2011) and refuting (Broos et al., 2012; Schippers et al., 2012) an association. Although these findings are perhaps surprising given that heroin and cocaine addicts are also impulsive (Kirby and Petry, 2004; Moreno-López et al., 2012), it is possible that these clinical findings reflect the influence of chronic drug use and/or repeated cycles of drug bingeing and withdrawal on impulsivity levels. Consistent with this notion, both heroin (Schippers et al., 2012) and cocaine (Mendez et al., 2010; Paine et al., 2003; Roesch et al., 2007; Winstanley et al., 2009) exposure increases impulsivity in non-impulsive animals. However, in striking contrast, cocaine exposure in trait impulsive rats has the dramatic effect of decreasing impulsivity (Dalley et al., 2007), an effect that might be mediated by a restoration of dopaminergic function in the ventral striatum of this group of animals (D.C., Y. Hong, B.J., B. Everitt, T. Robbins, T. Fryer and J.W.D., unpublished findings).

The disparity between the contribution of impulsive action and impulsive choice to addiction susceptibility – and, as discussed previously, the apparent differences in neural correlates underlying these behaviours – brings to question whether impulsivity in these models reflects a unitary construct. To this point, studies have found that RHA rats demonstrate both enhanced impulsive action and choice (Moreno et al., 2010). Similarly, rats selected for high impulsivity on 5CSRTT were also impulsive on a delay-discounting task (Robinson et al., 2009). However, there is also evidence to suggest that impulsive action and impulsive choice reflect independent constructs. Thus, SHRs were found to be impulsive on a delay-discounting task (Adriani et al., 2003) but not a 5CSRTT (van den Bergh et al., 2006a), and no correlation was observed between the performance of Wistar rats on a stop-signal or 5CSRTT and delay discounting (Broos et al., 2012), a dissociation that also extends to humans (Broos et al., 2012). It is possible that impulsive action and impulsive choice represent distinct but related constructs with overlapping mechanisms, making it possible for the two types of impulsivity to co-exist without being directly correlated. To this effect, although these two forms of impulsivity reflect deficits in ‘failing to wait’ tasks assessing impulsive choice also incorporate a value assessment. Therefore, deficits in performance can also be related to mechanisms involved in interpreting reward value that are distinct from those involved in ‘waiting’ *per se*. Interestingly, the neural substrates involved in coding reward value are similar to those involved in impulsivity (reviewed by Levy and Glimcher, 2012). Thus, it might be possible for an individual to be impulsive on delay-discounting choice tasks without being impulsive on motor tasks (e.g. stop-signal), but not vice versa.

Impulsivity seems to be one of several behavioural endophenotypes associated with addiction-like behaviour. Others

Table 2. Selected references for effects of systemic and region-specific pharmacological interventions on impulsive responding in rats

Transmitter or receptor	Pharmacological agent	Region	Effect on impulsive action (motor disinhibition)	Effect on impulsive choice (delay discounting)
Dopaminergic				
DA	Amphetamine (DA agonist)	Systemic	↑ (Pattij et al., 2007b)	↓ (Wade et al., 2000)
	6-hydroxydopamine (DA reduction)	NAc	↑ (Cole and Robbins, 1987)	= (Winstanley et al., 2005)
	Methylphenidate (DA/NA agonist)	NAc core	↑ (Economidou et al., 2012)	
		NAc shell	= (Economidou et al., 2012)	
D1	SCH 23390 (D1 antagonist)	Systemic		= (Wade et al., 2000)
		NAc core	↓ (Pattij et al., 2007b)	
		NAc shell	↓ (Pattij et al., 2007b)	
		DS	↓ (Eagle et al., 2011)	
	mPFC		↑ (Loos et al., 2010)	
SKF38393 (D1 agonist)	NAc	↑ (Pezze et al., 2007)		
D2/D3	Raclopride (D2/D3 antagonist)	Systemic		↑ (Wade et al., 2000)
	Eticlopride (D2/D3 antagonist)	NAc core	= (Pattij et al., 2007b)	
		NAc shell	= (Pattij et al., 2007b)	
	Sulpiride (D2/D3 antagonist)	DS	↑ (Eagle et al., 2011)	
Serotonergic				
5HT	SERT knock-out rat	Global	↑ (Homberg et al., 2007)	
	Fluoxetine (5HT reuptake inhibitor)		↓ (Bizot et al., 1999)	
5HT1A	Citalopram (5HT reuptake inhibitor)		↓ (Baarendse and Vanderschuren, 2012)	= (Baarendse and Vanderschuren, 2012)
	8-OH-DPAT (5HT1A agonist)	Systemic		↓ (Bizot et al., 1999)
	WAY100635 (5HT1A antagonist)			↑ (Bizot et al., 1999)
5HT2A	M100907 (5HT2A antagonist)		↓ (Winstanley et al., 2003)	
		mPFC	↓ (Winstanley et al., 2003)	
		Infralimbic cortex	= (Robinson et al., 2008a)	
		Prelimbic cortex	= (Robinson et al., 2008a)	
	DS	↓ (Agnoli and Carli, 2012)		
	Ketanserin (5HT2A antagonist)			= (Talpos et al., 2006)
5HT2C	SB242084 (5HT2C antagonist)	Systemic	↑ (Winstanley et al., 2004b)	
	Ro60-0175 (5HT2C agonist)		↓ (Fletcher et al., 2011)	
		DS	↓ (Agnoli and Carli, 2012)	
	SB242084 (5HT2C antagonist)	NAc	↑ (Robinson et al., 2008a)	
Noradrenergic				
NA	Atomoxetine (NAT reuptake inhibitor)	Systemic	↓ (Paterson et al., 2011)	↓ (Robinson et al., 2008b)
		NAc core	= (Economidou et al., 2012)	
		NAc shell	↓ (Economidou et al., 2012)	
α2	Guanfacine (α2 antagonist)	Prelimbic cortex	↑ (Bari et al., 2011)	
Glutamatergic				
Glutamate NMDA	MK801 (NMDA antagonist)	Systemic	= (Paine et al., 2007)	
	3-(R)-2-carboxypiperazin-4-phosphonic acid (NMDA antagonist)	Infralimbic cortex	↑ (Murphy et al., 2012)	

Table continued on next page

Table 2. Continued

Transmitter or receptor	Pharmacological agent	Region	Effect on impulsive action (motor disinhibition)	Effect on impulsive choice (delay discounting)
Glutamatergic				
mGluR1	EMQMCM (mGluR1 antagonist)	Systemic	= (Semenova and Markou, 2007)	↓ (Sukhotina et al., 2008)
mGluR2/3	LY341495 (mGluR2/3 antagonist)			
	LY487379 (mGluR2/3 antagonist)		↓ (Nikiforuk et al., 2010)	
Opioidergic				
δ-opioid	Naltrindol (δ-antagonist)	Systemic	= (Wiskerke et al., 2011)	= (Wiskerke et al., 2011)
κ-opioid	Nor-BI (κ-antagonist)		= (Wiskerke et al., 2011)	= (Wiskerke et al., 2011)
μ-opioid	Naloxone (μ-antagonist)	NAc core	↓ (Wiskerke et al., 2011)	= (Wiskerke et al., 2011)
		NAc shell	= (Wiskerke et al., 2011)	
Cholinergic				
ACh	Nicotine (nACh agonist)	Systemic	↑ (Grottick and Higgins, 2000)	↑ (Kolokotroni et al., 2011)
nACh α2β4	Dihydro-beta-erythroidine (nACh α2β4 antagonist)		Infralimbic cortex	↓ (Tsutsui-Kimura et al., 2010a)
		Prelimbic cortex	↓ (Tsutsui-Kimura et al., 2010b)	
nACh α7	nAChα7 receptor knockout mouse	Global	= (Tsutsui-Kimura et al., 2010b)	
			↑ (Hoyle et al., 2006)	
Cannabinoid				
Cannabinoid CB1	SR141716A (CB1 antagonist)	Systemic	↓ (Pattij et al., 2007a)	

↑ and ↓ denote an increase and decrease in impulsive responding, respectively; = denotes no effect. DA, dopamine; 5HT, serotonin; NA, noradrenaline; NMDA, N-methyl-D-aspartate; mGluR, metabotropic glutamate receptor; ACh, acetylcholine; nACh, nicotinic acetylcholine; NAc, nucleus accumbens; mPFC, medial prefrontal cortex; DS, dorsal striatum. For a comprehensive review see Eagle and Baunez, and Winstanley (Eagle and Baunez, 2010; Winstanley, 2011).

include novelty reactivity (Piazza et al., 1990), novelty preference (Belin et al., 2011), anxiety (Dilleen et al., 2012) and sign-tracking (Flagel et al., 2010). Although novelty-reactive rats demonstrate enhanced measures of impulsive action, and acquire a conditioned approach response to an appetitive stimulus [i.e. sign-trackers (Flagel et al., 2010)], trait impulsive animals show no obvious heightened sensitivity to novelty (Dalley et al., 2007; Molander et al., 2011), nor do they differentially acquire appetitive conditioned approach compared with low-impulsive rats (Robinson et al., 2009). However, both RHA and rats impulsive on the 5CSRTT show a preference for novel objects and contexts (Giorgi et al., 2007; Molander et al., 2011), which might reflect a reduction in novelty-induced anxiety in these animals (Duclot et al., 2011). Indeed, it has been suggested that anxiety is inversely related to impulsivity (Schneider et al., 2012), an intriguing relationship considering that both impulsivity and anxiety predict addiction vulnerability. Although there is some evidence to suggest that anxiolytics enhance impulsivity (Bizot et al., 1988; Evenden and Ryan, 1996), it is unclear whether this is due to an effect to reduce anxiety, given that doses shown to be anxiolytic had no effect on premature responding in these animals (Molander et al., 2011). Furthermore, there is little evidence to suggest that trait impulsive animals are anxious (Loos et al., 2009); thus, their preference for novelty might simply reflect an underlying deficit in behavioural inhibition.

However, trait-like impulsivity does predict the emergence of compulsive cocaine taking in rodents (Belin et al., 2008), defined by the persistence of drug intake despite punishing feedback

(Everitt et al., 2008). Furthermore, impulsive SHR and RHA lines show compulsive drinking on a schedule-induced polydipsia (SIP) task (Ibias and Pellón, 2011; Moreno et al., 2010), whereas individual variation in SIP predicts impulsivity in delay-discounting (Cardona et al., 2011) and 5CSRTT (Moreno et al., 2012). Collectively, these findings demonstrate that impulsivity, in its various forms, is a vulnerability marker for the development of compulsive drug taking. However, it remains unclear whether impulsivity and compulsivity subtypes co-exist in the same individual, or whether they are separable entities that are serially expressed in a manner dependent on drug-induced plasticity in the PFC and striatum (Dalley et al., 2011).

Implications for addiction

Findings in naturally impulsive rodents suggest that impulsivity represents a susceptibility factor for addiction rather than occurring directly as a consequence of chronic drug use. Clinical studies demonstrating enhanced impulsivity in the non-drug-using siblings of chronic stimulant abusers support this assertion (Ersche et al., 2012; Ersche et al., 2010). Given this, it is possible that treating impulsivity might prevent the development of compulsive drug use and/or the occurrence of relapse in susceptible individuals, although clinical and preclinical studies confirming the efficacy of this therapeutic intervention are still required. However, atomoxetine, a selective noradrenaline reuptake inhibitor, reduces impulsive responding in highly impulsive rats (Fernando et al., 2012), as well as decreasing cocaine-seeking in these animals (Economidou et al.,

2009). Moreover, clinical trials have provided some evidence for enhanced rates of abstinence following treatment with the related drug reboxetine in cocaine-dependent patients (Szerman et al., 2005).

Psychostimulant drugs have been shown to reduce some forms of impulsivity in animals (Sagvolden and Xu, 2008; Wooters and Bardo, 2011). Furthermore, cocaine self-administration has been shown to normalise excessive impulsive responding in rats (Dalley et al., 2007). A plausible hypothesis, given that impulsive animals are susceptible to compulsive cocaine self-administration, follows that drug intake potentially represents a form of 'self-medication' in impulsive subjects. Indeed, this might correct an apparent hypodopaminergic state in these animals, which itself predicts increased cocaine self-administration (Michaelides et al., 2012; Nader et al., 2006). It should be noted, however, that cocaine reduces striatal binding of the D2-like PET ligand [¹⁸F]fluorocleobopride (Nader and Czoty, 2005), an effect that might in fact drive continued cocaine use, reflecting the cycle of chronic cocaine abuse observed in addicts. The observed ventral-to-dorsal shift in dopaminergic dysfunction that results from prolonged cocaine self-administration (Porrino et al., 2004) has been suggested to underlie the development of maladaptive habit learning in addiction (Everitt and Robbins, 2005). There is also evidence implicating D2/D3 function in the dorsal striatum in behavioural inhibition (e.g. Ghahremani et al., 2012), providing another avenue through which D2/D3 receptor dysfunction might contribute to the link between impulsivity and addiction. At least in rats, impulsivity on the 5CSRTT does not seem to be related to D2/D3 receptor function in the dorsal striatum (Dalley et al., 2007); however, D2/D3 receptor availability in this region has been shown to predict irrational, biased decision making in rats (Cocker et al., 2012), a finding of possible relevance to behavioural addictions such as pathological gambling.

Conclusions

Animal models of impulsivity have provided significant insight into the underlying neurobiological, genetic and environmental contributions to impulsivity as a behavioural endophenotype, and as a susceptibility marker for addiction. Such findings have implicated dysfunction in monoaminergic corticostriatal systems in the expression of impulsivity and have specifically identified a putative involvement of striatal D2/D3 receptors. Further refinement of such models are likely to reveal currently unknown mechanisms underlying the apparent causal relationship between impulsivity and addiction, thereby informing the development of new therapeutic strategies for disorders of behavioural control.

COMPETING INTERESTS

None to declare.

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