

In search of predictive endophenotypes in addiction: insights from preclinical research

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/gbb.12265

Abstract

Drug addiction is widely recognised to afflict some but not all individuals by virtue of underlying risk markers and traits involving multifaceted interactions between polygenic and external factors. Remarkably, only a small proportion of individuals exposed to licit and illicit drugs develop compulsive drug seeking behavior, maintained in the face of adverse consequences, and associated detrimental patterns of drug intake involving extended and repeated bouts of binge intoxication, withdrawal, and relapse. As a consequence research has increasingly endeavoured to identify distinctive neurobehavioral mechanisms and endophenotypes that predispose individuals to compulsive drug use. However, research in active drug users is hampered by the difficulty in categorising putatively causal behavioral traits prior to the initiation of drug use. By contrast, research in experimental animals is often hindered by the validity of approaches used to investigate the neural and psychological mechanisms of compulsive drug-seeking habits in humans. Herein, we survey and discuss the principal findings emanating from preclinical animal research on addiction and highlight how specific behavioral endophenotypes of presumed genetic origin (e.g. trait anxiety, novelty preference and impulsivity) **differentially contribute to** compulsive forms of drug seeking and taking and, in particular, how these differentiate between different classes of stimulant and non-stimulant drugs of abuse.

Key words: substance use disorder; anxiety; impulsivity; sensation-seeking; novelty preference; psychostimulants; opiates; alcohol

Introduction

Drug addiction is a complex neuropsychiatric disorder that manifests in a comparatively small subset of people exposed repeatedly to drugs (Anthony *et al.*, 1989, Anthony *et al.*, 1994, Degenhardt *et al.*, 2008). **Addicted individuals place a substantial economic and social burden, estimated to cost the UK more than 40 billion pounds each year (Justice, 2013). However,** despite decades of animal and clinical research the etiological mechanisms and pathophysiology of this progressive and debilitating disorder remain surprisingly poorly understood. Nevertheless, the shift from recreational to compulsive drug seeking, a hallmark of addiction or **substance use disorder** (American Psychiatric Association, 2013), is widely regarded to depend on several interacting variables encompassing specific behavioral traits, environmental triggers (e.g. stress) and unremitting drug use (Kreek *et al.*, 2012, Uhl, 2004, Uhl & Grow, 2004, Wong & Schumann, 2008). Determining the intricate interplay between these variables presents a formidable barrier to understanding the origin of addiction in afflicted individuals (Meyer-Lindenberg & Weinberger, 2006).

Addiction is commonly allied with distinct behavioral traits, co-morbid psychiatric disorders and cognitive impairment (Rogers & Robbins, 2001). In particular, the traits of anxiety, sensation-seeking and impulsivity are strongly linked with drug abuse (Franques *et al.*, 2000, Sher *et al.*, 2000, Terracciano *et al.*, 2008, Zuckerman, 1986) and often preferentially to specific classes of abused drug (Ball *et al.*, 1998, Clapper *et al.*, 1994, Conway *et al.*, 2002, Franques *et al.*, 2000, Gossop, 1978, Greene *et al.*, 1993, Labouvie & Mcgee, 1986, Schinka *et al.*, 1994, Terracciano *et al.*, 2008, Zuckerman, 1986). However, in individuals addicted to drugs, where more than one drug is frequently abused, it is almost impossible to disambiguate the causal trajectory of premorbid, drug-naïve, traits from the effects of on-going drug use itself (Rogers & Robbins, 2001). As a result animal experimental approaches to addiction have increasingly become more sophisticated in recent years to more accurately reflect ‘real world’ *compulsive* drug use beyond simple reinforcement mechanisms (Belin *et al.*, 2009a, Belin *et al.*, 2011a, Belin & Everitt, 2008,

Belin *et al.*, 2008, Belin-Rauscent *et al.*, 2015, Deroche-Gamonet *et al.*, 2004, Kasanetz *et al.*, 2010, Kasanetz *et al.*, 2013, Pelloux *et al.*, 2007, Vanderschuren & Everitt, 2004). These approaches enable well-controlled, within-subject, longitudinal studies to be carried out with high construct and predictive validity (Belin-Rauscent & Belin, 2012, Geyer *et al.*, 1995) ultimately to investigate biological and genetic mechanisms underlying drug-prone behavioral traits and constructs. Here, we survey the discoveries made using these clinically-informed approaches, future research directions, and the translational relevance of this work for human addiction.

Measuring drug taking and drug relapse in experimental animals

Whilst animal models can never replicate entirely the complex social and often personal reasons why people start using and eventually abusing drugs (Comeau *et al.*, 2001, Khantzian, 1997), they nevertheless provide a rigorous means to precisely control environmental context, drug exposure, and behavioral and cognitive processes prior to drug exposure. They also allow detailed neural interventions to be carried out to establish the causal influences of putative neural loci and, in turn, the cellular and molecular substrates of addiction. Experimental approaches in animals thus provide a valuable means to investigate the different stages of addiction (Belin-Rauscent *et al.*, 2015, Everitt, 2014) including the initiation and maintenance of drug taking, accompanying bouts of drug bingeing and escalation, and later the ‘switch’ to compulsive drug use defined operationally by the persistence of drug-seeking despite punishment (Belin-Rauscent *et al.*, 2015).

Over the last decade pre-clinical research has strived to better integrate one or more defining dimensions of addiction according to the Diagnostic and Statistical Manual (American Psychiatric Association, 2013). This research has paved the way to identify specific phenotypes and markers underlying reinstatement of extinguished instrumental seeking responding (Bossert *et al.*, 2005, Shaham & Miczek, 2003), relapse to drug-seeking (Tran-Nguyen *et al.*, 1998), loss-of-control over drug intake (Ahmed & Koob, 1998, Ahmed

& Koob, 2005), habitual and compulsive cocaine seeking (Belin & Everitt, 2008, Economidou *et al.*, 2009, Everitt & Robbins, 2000, Giuliano *et al.*, 2015, Murray *et al.*, 2014, Pelloux *et al.*, 2007, Vanderschuren & Everitt, 2005), and individual variability in addiction-like behavior (Belin *et al.*, 2009a, Belin *et al.*, 2011a, Belin & Deroche-Gamonet, 2012, Deroche-Gamonet *et al.*, 2004).

Drug self-administration

Drugs abused by humans have powerful reinforcing effects (Belin *et al.*, 2009b, O'Brien *et al.*, 1992a, Robbins & Everitt, 2002, White, 1996). This fundamental capacity of addictive substances is widely and routinely investigated using the drug self-administration paradigm where rats, monkeys and other animals learn to respond contingently (e.g. on a lever) to obtain a drug delivered intravenously, orally or even directly into the brain (e.g. David *et al.*, 2006, Goldberg *et al.*, 1969, Miles *et al.*, 2003, Parada *et al.*, 1994, Spealman & Goldberg, 1978, Weeks, 1962). In many drug self-administration paradigms drug delivery is predicted by the contingent presentation of a stimulus that becomes, through Pavlovian conditioning, a conditioned stimulus (CS). Assessing the acquisition of drug self-administration has provided valuable insights into the neural substrates that support and regulate volitional drug-taking behavior (Chao & Nestler, 2004). **By increasing the response demand for each drug infusion, effected using a progressive-ratio (PR) schedule, the motivation for drugs can also be evaluated (Belin & Deroche-Gamonet, 2012, Richardson & Roberts, 1996).** However, such reinforcement schedules alone, where animals receive drug after every response, or after every ratio of responses, fail to capture the propensity of addicted individuals to relapse and persistently seek drugs.

Reinstatement

Drug addicted individuals show a high propensity to relapse, even after protracted abstinence (American Psychiatric Association, 2013). This defining aspect of addiction is commonly modelled in animals using two main empirical approaches: (i) extinction-reinstatement, developed initially by Jane Stewart and colleagues (De Wit & Stewart, 1981, De Wit & Stewart, 1983); and (ii) procedures based on abstinence-relapse (See *et al.*, 2007).

Reinstatement of responding for drug can be elicited by stress, low priming doses of drug, and by the presentation of drug-associated cues (Bossert *et al.*, 2005, Capriles *et al.*, 2003, De Wit & Stewart, 1981, De Wit & Stewart, 1983, Fuchs *et al.*, 2004, Fuchs *et al.*, 2008, Fuchs *et al.*, 1998, Knackstedt & Kalivas, 2009, Marchant *et al.*, 2013b, Shalev *et al.*, 2002, Torregrossa & Kalivas, 2008, Zhou & Kalivas, 2008). In the extinction-reinstatement paradigm (Rocha & Kalivas, 2010), animals experience a series of extinction sessions following a short period of drug self-administration; this results in a progressive decline in responding. Following extinction, responding for drug is reinstated by either a stressful stimulus, a priming injection of drug, a drug-paired CS or by placing the animal in a drug-conditioned environment. The neural circuits of reinstatement have been extensively mapped and include structures within the extended amygdala, prefrontal cortex and mesolimbic dopamine (DA) system (De Wit & Stewart, 1981, De Wit & Stewart, 1983, Kalivas & Mcfarland, 2003, Shalev *et al.*, 2002).

Forced abstinence-induced relapse

In abstinence-relapse procedures (See *et al.*, 2007), animals undergo a forced period of abstinence following a brief period of drug self-administration. Thereafter they are maintained in their home cage until being exposed again to the self-administration chamber where they are tested under extinction. Whereas reinstatement procedures involve the nucleus accumbens (NAcb) and dopaminergic and glutamatergic inputs to this region, abstinence-induced relapse to drug-seeking depends instead on the dorsolateral striatum (Fuchs *et al.*, 2006, See *et al.*, 2007).

Preclinical models of relapse have also been developed that provide a closer correspondence to *voluntary* abstinence and the compulsive forms of relapse typical of human addicted to drugs (Ducret *et al.*, 2015, Economidou *et al.*, 2009, Marchant *et al.*, 2014, Marchant *et al.*, 2013a). **In such procedures rats are trained to self-administer the drug with an aversive stimulus (e.g. foot-shock) presented in the same or different context such that rats abstain from responding.** In such settings, considerable variability exists in the rate of decrease in instrumental responding among different rats (Economidou *et al.*, 2009, Marchant *et al.*, 2014) and this can be exploited to investigate neurobiological mechanisms of both self-imposed abstinence and the resumption of instrumental responding (relapse) when the aversive stimulus is removed.

Measuring drug addiction-like behavior in experimental animals

There has been considerable progress made in recent years in developing novel experimental approaches to the study of ‘addiction’. In a general sense such approaches attempt to capture not only the persistence of drug seeking and drug taking under punishment but also the evident vulnerability of sub-populations of individuals to switch from controlled to compulsive drug use (Belin-Rauscent *et al.*, 2015).

Drug-seeking

Drug addicts increasingly develop a preoccupation with drug use and spend considerable periods of time foraging to gain access to drugs. This aspect of drug seeking can be captured in animals by implementing schedules of reinforcement that separate drug seeking from drug taking responses **and by the conditioned place preference (CPP) assay. CPP is widely used to elucidate the mechanisms supporting appetitive associative properties of addictive drugs (Blander *et al.*, 1984, Stewart & Grupp, 1981, Stolerman, 1985, White & Carr, 1985) but has limited utility in probing compulsive drug seeking and therefore is not considered further in this article.** Other approaches include two-link heterogeneous

chained schedules of reinforcement and second order schedules of reinforcement. The two-link heterogeneous chained schedule involves responding on (e.g.) one lever, designated the seeking link, to gain access to a drug taking lever (the second link). This procedure has the distinct advantage of clearly separating two instrumental components of drug seeking and taking, which involve dissociable neural and psychological processes (Belin *et al.*, 2009b, Everitt & Robbins, 2005). In second-order schedules of reinforcement (Goldberg, 1973) a CS is presented response-contingently, usually under a fixed-ratio schedule, during an overall fixed interval or fixed ratio schedule for the primary reinforcer; this has the dramatic effect of enhancing and maintaining drug seeking responses during the inter-reinforcement interval (Arroyo *et al.*, 1998, Belin *et al.*, 2011b, Belin & Everitt, 2008). Thus, under a second-order schedule of reinforcement, a strong contingency exists between the instrumental response and the presentation of the CS occasioned by the relatively weaker contingency between instrumental behaviour and delivery of drug. Such schedules facilitate the development of habitual stimulus-response (S-R) control over instrumental responding (Adams & Dickinson, 1981).

Compulsive drug seeking and taking

Compulsive disorders such as addiction involve the uncontrollable and irresistible urge to perform a behavior, often to relieve anxiety or stress, irrespective of whether the behavior is rationale or not and results in adverse outcomes (Everitt & Robbins, 2015, Koob *et al.*, 1998). In particular, virtually all abused drugs are neurotoxic and produce with protracted use severe neurological complications. Such effects would normally be expected progressively to devalue a drug reinforcer and facilitate abstinence. Critically, however, despite often acknowledging the deleterious impact of chronic drug abuse, addicts rarely achieve spontaneous and enduring voluntary abstinence. Remarkably, this emergent tendency to discount drug-associated adversity also extends to rodents. Thus, although responding for

food is markedly affected by pairing its ingestion with illness caused by the systemic injection of lithium chloride, similar devaluation of orally-administered alcohol and cocaine does not demonstrably decrease drug-seeking behavior (Corbit *et al.*, 2012, Cunningham *et al.*, 2000, Dickinson *et al.*, 2002). Moreover, Vanderschuren and Everitt (2004) established that the presentation of a Pavlovian conditioned fear stimulus after an extended self-administration training history failed to suppress cocaine self-administration, whereas after a brief cocaine-taking history, it did. Thus, while instrumental behaviour directed at obtaining drugs may be initially a flexible, goal-directed pursuit, following prolonged drug exposure, drug-seeking becomes increasingly insensitive to signals of punishment, thereby revealing its compulsive character. However, even after moderate drug exposure, a sub-group of rats (~20%) noticeably show enhanced resistance to punishment with minimal or no suppression of drug-seeking under punishment (Pelloux *et al.*, 2007). Thus, compulsive drug-seeking in rats appears to depend, as in humans, on the duration and quantity of drug use together with interacting individual vulnerability mechanisms.

Loss-of-control over drug taking

A major defining feature of addiction is escalated drug use that develops with protracted drug use. This phenomenon can be modelled in rats given either short access (“ShA”) or long access (“LgA”) to intravenous cocaine (Ahmed & Koob, 1998) or heroin (Ahmed & Koob, 2005) self-administration. ShA to addictive drugs generally results in stable levels of self-administration such that plasma drug levels are regulated within an optimal level of reinforcement (Zernig *et al.*, 2007). By contrast, LgA drug exposure results in a steady escalation in drug self-administration and higher rates of responding for drug during the first hour of each session (Ahmed & Koob, 1998). Notably, escalated drug intake is associated with higher resistance to both shock-induced and conditioned suppression of drug self-administration (Ahmed *et al.*, 2000, Pelloux *et al.*, 2007) suggesting that drug-induced neural plasticity mechanisms may contribute to some aspects of compulsive drug taking. **Moreover,**

after extended access to cocaine, only a subgroup of animals (~24%) showed minimal or no shock-induced suppression of drug taking (Pelloux *et al.*, 2007).

However, the LgA model does assume that all subjects exposed to cocaine and other drugs develop compulsive drug intake, a prediction at odds with the notion of individual vulnerability affecting far fewer individuals than those exposed initially to drugs (Anthony *et al.*, 1994). Moreover, **only roughly 40% of rats** subjected to LgA heroin robustly show escalated self-administration (Mcnamara *et al.*, 2010) and rats still prefer saccharine over cocaine despite showing greatly elevated cocaine self-administration with extended access (Lenoir *et al.*, 2007). These findings suggest that schedule-induced escalation of drug intake captures one aspect of addiction, namely the use of drug in larger amounts, but in isolation this phenomenon is not sufficient to explain the development of compulsive drug taking in subsets of vulnerable individuals.

The concept of inter-individual vulnerability to addiction has been substantiated by operationalising three diagnostic criteria of DSM-IV (American Psychiatric Association, 2000) in rats. These include: (i) an inability to refrain from drug seeking; (ii) increased motivation for the drug; (iii) maintained drug use despite negative consequences, and assessed, respectively, by drug-seeking during periods when the drug is not available and signalled as so; increased break points under a progressive-ratio schedule of reinforcement; persistent drug taking despite punishment by contingent foot-shocks (Belin *et al.*, 2008, Deroche-Gamonet *et al.*, 2004). By assigning a score to each criteria an ‘addicted’ profile can be defined by the 3 criteria rat (3crit) that show high scores for each of the three addiction-like criteria; these represent approximately 20% of all animals tested (Belin *et al.*, 2011a). By contrast, animals showing low scores (i.e. 0 criteria or ‘0crit’ subjects) are classified as resilient to addiction (Belin & Dalley, 2010, Belin & Deroche-Gamonet, 2012, Deroche-Gamonet *et al.*, 2004).

Although 3crit rats do not differ significantly from 0crit rats in terms of acquiring cocaine self-administration (Belin *et al.*, 2009a, Belin *et al.*, 2011a, Belin *et al.*, 2008,

Deroche-Gamonet *et al.*, 2004), 3crit rats eventually develop higher motivation for the drug, an inability to refrain from drug-seeking, and resistance to punishment (Belin *et al.*, 2009a, Belin *et al.*, 2011a, Belin *et al.*, 2008, Deroche-Gamonet *et al.*, 2004). More importantly, although selected on three addiction-like behaviours, 3crit rats also show enhanced escalation of cocaine self-administration and an increased for relapse compared with 0crit rats (Belin *et al.*, 2009a, Deroche-Gamonet *et al.*, 2004). This subset of animals thus shows additional hallmarks of vulnerability to addiction that depend on chronic drug experience.

Vulnerability traits

Epidemiological research has unequivocally demonstrated a relationship between drug use in humans and the traits of anxiety (Conway *et al.*, 2002, Forsyth *et al.*, 2003, O'leary *et al.*, 2000, Skinstad & Swain, 2001), impulsivity (Roberts, 2000, Zilberman *et al.*, 2007) and sensation-seeking (Arnett, 1994, Franques *et al.*, 2000, Hanson *et al.*, 2008, Moeller *et al.*, 2002, Petry *et al.*, 2002, Zuckerman, 1986). Such traits are associated with addiction to psychostimulants (Moeller *et al.*, 2002, Semple *et al.*, 2005), opiates (Madden *et al.*, 1997, Maremmani *et al.*, 2009), alcohol (Zuckerman, 1990) and tobacco (Petry, 2001). Significantly, however, the expression of these traits varies throughout the lifespan (Bickel *et al.*, 1999) and during different stages of the addiction cycle (Kreek *et al.*, 2005). Thus it is exceedingly difficult to determine how dynamically-expressed traits such as these promote and interact with repeated drug use to accelerate drug addiction in humans. Furthermore, recent evidence indicates that some traits may have very specific effects on drug taking activities. Thus, although the traits of sensation-seeking and impulsivity are present in drug dependent individuals, sensation-seekers still maintain some control over their drug intake, unlike impulsive people (Ersche *et al.*, 2013). Furthermore trait-like impulsivity in rats predicts behavioral features of addiction-like behavior to cocaine but not heroin (Belin *et al.*, 2008, Dalley *et al.*, 2007, Mcnamara *et al.*, 2010). In the remaining sections we review the key findings originating from research in animals that demonstrate the critical dependence of

specific addiction-like behaviors on various precursor ‘traits’.

Anxiety

Highly-anxious individuals may use drugs as part of a coping strategy to gain relief by self-regulating affective distress states (Khantzian, 1985, Khantzian, 2013, Lejuez *et al.*, 2008). Indeed alcohol use disorders and anxiety are highly comorbid in humans (Ipser *et al.*, 2015). This form of emotional self-medication may underlie the initiation of drug use, subjective states underlying craving (Lejuez *et al.*, 2008, Sherman *et al.*, 1989, Sinha, 2001) and the continuation of drug use as a way to mitigate withdrawal symptoms (Khantzian, 1985, Khantzian, 2013, Spear, 2000).

Pre-clinically, anxiety is typically assessed using procedures that exploit the natural fear of animals to open and brightly lit spaces. The elevated plus maze (EPM) (Pellow *et al.*, 1985, Pellow & File, 1986) is commonly used for this purpose with anxiety measured as the preference of animals for closed (protected) versus open arms and increased self-grooming behavior (**Fig.1**). High anxiety on this task predicts the more rapid emergence of a conditioned place preference for cocaine (Pelloux *et al.*, 2009), higher break points to self-administer this stimulant (Homberg *et al.*, 2002), but see (Bush & Vaccarino, 2007), and increased preference for alcohol (Henniger *et al.*, 2002, Spanagel *et al.*, 1995). Additionally, anxious rats on the EPM more readily escalate cocaine but not heroin self-administration compared with low-anxious rats (Dilleen *et al.*, 2012). This apparent but surprising relationship between anxiety and subsequent vulnerability to escalate cocaine intake may result from an increased tolerance to the anxiogenic effects of high-dose cocaine (Paine *et al.*, 2002) and/or an enhanced anxiolytic effect of low doses of cocaine (Muller *et al.*, 2008).

Withdrawal severity may also play a role in the development of alcoholism and drug abuse specifically by encouraging further drug use to relieve anxiety (Holter *et al.*, 1998). Work in mice selectively bred for high and low handling-induced convulsions after chronic ethanol treatment appears to support this idea (Atkins *et al.*, 2000). Thus, convulsion-prone

mice showed higher levels of baseline anxiety and were more sensitive to the anxiolytic effects of alcohol than convulsion-resistant mice, suggesting that convulsion-prone animals may be genetically predisposed to severe alcohol withdrawal symptoms. However, although mice selectively bred for high drinking in the dark (the HDID line) also showed reduced anxiety after drinking, no genetic relationship was found between alcohol drinking and anxiety (Barkley-Levenson & Crabbe, 2015). Thus, anxiety state and alcohol-induced anxiolysis does not explain why HDID mice maintain higher rates of drinking. However, though beyond the scope of this article, substantial findings in knockout and transgenic mice implicate a major role of the stress hormone corticotropin-releasing factor in determining high rates of alcohol consumption and alcohol-seeking during abstinence (for a recent review see Phillips *et al.*, 2015).

Novelty-seeking

Novelty/sensation-seeking is a multifaceted behavioral construct (Arnett, 1994) defined as the tendency to pursue intense emotional experiences (Zuckerman, 1974) and conceptualized as a heritable tendency towards exploration and excitement in response to novelty (Cloninger *et al.*, 1993). Studies in humans have yielded unequivocal evidence that novelty/sensation-seeking co-exists in individuals with substance use disorder (Gerra *et al.*, 2004, Hittner & Swickert, 2006, Noel *et al.*, 2011) and predicts risk for the initiation of drug use (Nees *et al.*, 2012, Sargent *et al.*, 2010, Spillane *et al.*, 2012, Stephenson & Helme, 2006). However, although sensation-seeking is not present in non-affected siblings of drug-addicts, and unlikely therefore to be a candidate endophenotype in addiction (Ersche *et al.*, 2010) it is present in regular drug users apparently able to maintain controlled drug use (Ersche *et al.*, 2013).

Several procedures have been implemented to assess novelty-seeking behavior in animals. These generally involve assessing the preference of rats for novel versus familiar environments using activity chambers that differ in light intensity, openness, colour and

texture (**Fig.1**). Notably, using a variant of this procedure, the high novelty preference (HNP) ‘trait’ in rats was found to strongly associate with individual vulnerability to develop compulsive cocaine self-administration (Belin *et al.*, 2011a). Interestingly, however, novelty reactivity in non-human primates, as assessed by latencies to touch a novel object, has been linked with social dominance, a trait generally associated with a low vulnerability for cocaine abuse (Czoty *et al.*, 2010). Indeed this form of novelty-seeking may be analogous to the high-responder (HR) rat, discussed below.

Piazza *et al.* (1989) were among the first to consider inter-individual differences in the way in which animals respond to drugs and thus the concept of “addiction vulnerability” in preclinical models. In this procedure, the sensation-seeking trait is assumed by the locomotor reactivity of drug-naïve animals in a novel, inescapable environment (Dellu *et al.*, 1996) (**Fig.1**). Based on inter-individual differences in locomotor response over 2 hours animals are classified as either HRs or low responders (LRs) based on a median division (Piazza *et al.*, 1989). HR rats show a greater propensity to acquire psychostimulant self-administration (Piazza *et al.*, 1989), more readily self-administer low doses of psychostimulants than LR rats (Belin *et al.*, 2008, Piazza *et al.*, 1989) and self-administer more cocaine per unit infusion dose than LR rats (Piazza *et al.*, 2000). Importantly, the dimension of novelty/sensation-seeking is heritable in outbred rats and is associated with reduced anxiety compared with LR rats (Stead *et al.*, 2006).

Impulsivity

Impulsivity has emerged as a key dimensional construct in psychiatry, defined by the tendency for premature, poorly planned, and unduly risky actions (De Wit, 2009, Evenden, 1999, Lejuez *et al.*, 2010, Potenza & De Wit, 2010). Since impulsivity is a heritable, disease-associated trait present in a number of clinical disorders of impulse control it has been championed as an endophenotype for gene discovery (Bevilacqua & Goldman, 2013).

Several taxonomies have been proposed to capture the evident multi-faceted nature of impulsivity from choice and motor/action impulsivity (Pattij & Vanderschuren, 2008, Uslaner & Robinson, 2006, Winstanley *et al.*, 2006), waiting and stopping impulsivity (Dalley *et al.*, 2011, Robinson *et al.*, 2009) to the triad of waiting, stopping and risk-based impulsivity (Robbins and Dalley, 2015). Understanding the neural and psychological heterogeneity of different impulsivity constructs is important not only in the context of psychiatric symptoms expressed in attention deficit/hyperactivity disorder (ADHD), schizophrenia, and depression but also in the self-regulation of reward-related behavior of relevance to drug addiction (De Wit, 2009, Jentsch & Taylor, 1999, Jupp & Dalley, 2014, Moeller *et al.*, 2001, Perry & Carroll, 2008). Indeed impulsive behavior is a common comorbid indication in addiction (Kreek *et al.*, 2005, Ohlmeier *et al.*, 2008, Swann *et al.*, 2002, Verdejo-Garcia *et al.*, 2008, Wills *et al.*, 1994, Wills *et al.*, 1998).

Impulsivity is often measured in humans using self-report scales (e.g. the Barrett Impulsiveness Scale or BIS) (e.g. Broos *et al.*, 2012). Such scales are convenient and standardised but are subjective and critically do not always reflect what is measured more objectively by translational methods used to dissociate and investigate different stages of impulse control, namely anticipatory behavior, reward discounting (temporal and probabilistic) and the cancellation of ongoing behavior (Ainslie, 1975, Dalley & Roiser, 2012, Swann *et al.*, 2002, Zuckerman & Neeb, 1979). Such methodologies, which include delayed gratification procedures (Hamilton *et al.*, 2015a, Hamilton *et al.*, 2015b), Go/No-Go performance, stop-signal reaction time (SSRT), differential reinforcement of low rates of responding ('DRL' schedules), and premature responding on analogues of the human continuous performance test have been used widely to investigate specific impulsivity constructs (Eagle *et al.*, 2008, Evenden, 1999, Voon *et al.*, 2014, Winstanley *et al.*, 2010) and predictive relations with drug reinforcement and addiction (Belin *et al.*, 2008, Carroll *et al.*, 2009, Dalley *et al.*, 2007, Diergaarde *et al.*, 2008). **In addition, risk-taking impulsivity associated with behavioral addictions such as pathological gambling (Robbins & Clark,**

2015) has been experimentally investigated using a rodent analogue of the Iowa Gambling Task (Zeeb *et al.*, 2009).

Jentsch and Taylor (1999) proposed that compulsive drug-seeking and drug-taking behavior resulted from chronic drug consumption that was suggested to diminish the capacity of the frontal cortex to suppress inappropriate (impulsive) conditioned and unconditioned responses elicited by drugs of abuse (Jentsch & Taylor, 1999). Many of the founding arguments of this theory continue to be supported by empirical research today but with the added elaboration of ‘trait-like’ variation in impulse control that precedes and causally influences the emergence of compulsive drug-seeking and taking (Belin *et al.*, 2008). Moreover, extending earlier findings that opiate and cocaine addicts discount future monetary rewards more so than non-users (e.g. Kirby & Petry, 2004, Madden *et al.*, 1997), Carroll and colleagues demonstrated in rats that impulsive choice on a delay-discounting task predicts the more rapid acquisition and escalation of cocaine self-administration (Anker *et al.*, 2009, Perry *et al.*, 2005, Perry *et al.*, 2008).

Our own research centres on a specific form of impulsive responding on the 5-choice serial reaction time task (5-CSRTT), akin to waiting impulsivity (Dalley *et al.*, 2011), and analogous to the human continuous performance test of sustained attention (Rosvold & Delgado, 1956, Wilkinson, 1963). In this task rats are required to monitor a horizontal array of apertures in order to detect a brief light stimulus and to refrain from responding before the onset of the stimulus (Robbins, 2002) (**Fig.1**). The accuracy of stimulus discrimination provides an index of attentional capacity, while premature responses - made before the presentation of the stimulus - are regarded as a form of impulsive behavior and hence a failure in impulse control (Mar & Robbins, 2007). Excessive and persistent failures to inhibit anticipatory responding on this task predicts the subsequent escalation of cocaine and nicotine self-administration (Dalley *et al.*, 2007, Diergaarde *et al.*, 2008), increased intake and sensitivity to sucrose (Diergaarde *et al.*, 2009), increased propensity for relapse following voluntary abstinence (Economidou *et al.*, 2009), and elevated cocaine self-administration

despite concurrent punishment with electric shock (Belin *et al.*, 2008). Thus, the high-impulsivity ‘trait’ predicts several hallmarks of addiction as distinct from recreational drug use.

Of particular significance was our observation that D2/3 receptor availability was reduced in the ventral (i.e. NAcB) but not dorsal striatum of high-impulsive rats prior to animals being exposed to cocaine (Dalley *et al.*, 2007). **Since PET studies in both human stimulant users (Lee *et al.*, 2009, Volkow *et al.*, 2001) and monkeys trained to self-administer cocaine (Nader *et al.*, 2006) report reduced D2/3 receptor availability in the caudate putamen (dorsal striatum), low D2/3 receptor availability in the ventral striatum may be a heritable, intermediate phenotype (i.e. endophenotype) associated with addiction vulnerability. Our findings have been substantiated in follow-up studies showing reduced D2/3 receptor expression and binding in the NAcB shell of high-impulsive rats (Besson *et al.*, 2009, Caprioli *et al.*, 2015, Jupp *et al.*, 2013). However, it remains unclear whether the high impulsivity ‘trait’ is associated with fewer autoreceptors and/or postsynaptic D2/3 receptors. In humans, trait impulsivity is associated with reduced D2/3 receptor availability in the midbrain (Buckholtz *et al.*, 2010) and studies in transgenic mice show that D2/3 autoreceptors critically modulate primary and conditioned drug reward (Bello *et al.*, 2011, Holroyd *et al.*, 2015). As well as exhibiting abnormalities in D2/3 receptor regulation we also observed reduced grey matter density, glutamate decarboxylase (catalysing GABA synthesis), and dendritic spine and microtubule markers in the NAcB core of high-impulsive rats (Caprioli *et al.*, 2014). Thus several, possibly interacting mechanisms at the level of the NAcB underlie the expression of the high impulsivity phenotype and these may be relevant to the evident vulnerability of impulsive rats to psychostimulant drugs.**

There is burgeoning evidence for familial and genetic origins of ADHD (Sullivan *et al.*, 2012) with rates of heritability as high as 75% (Faraone & Biederman, 2005, Faraone *et al.*, 2000). Evidence for a genetic basis of impulsivity has also been advanced in experimental animals using various inbred rodent strains that express high levels of impulsive behavior (Loos *et al.*, 2009, Moreno *et al.*, 2010, Russell *et al.*, 2005). Several functional genetic

variants associated with impulsive behavior have been identified, including the *HTR2B* gene encoding the 5-HT_{2B} receptor (Bevilacqua *et al.*, 2010). In a recent study (Dalley *et al.* unpublished data) using a six-generational inbred pedigree of low- and high-impulsive rats and 629 offspring we established that 5-CSRTT impulsivity segregates within families with heritability estimates ranging from 13 to 16%.

Using integrated transcriptional profiling and linkage analysis we also discovered that impulsivity was linked to a statistically-significant quantitative trait locus on chromosome 1 (LOD score 5.2) harbouring several candidate genes of interest for impulsivity. In particular, our analysis implicated *Grm5* (metabotropic glutamate receptor 5), a promising target to remediate impulsivity and stimulant drug-seeking (Chesworth *et al.*, 2013, Isherwood *et al.*, 2015, Liu *et al.*, 2008); *Sv2b* (synaptic vesicle glycoprotein 2B), implicated in regulating release at GABA-ergic and glutamatergic synapses (Bragina *et al.*, 2011); and *Sema4b* (semaphorin 4B), involved in the growth of neurons and formation of glutamatergic and GABA-ergic synapses (Paradis *et al.*, 2007). **Thus, drugs that target glutamatergic and GABA-ergic neurotransmission may have efficacy in blocking the ‘switch’ from controlled to compulsive drug use (and see Kalivas & Volkow, 2011).**

Sign-/goal-tracking

Cues associated with natural and drug rewards can through conditioning acquire motivational significance (Robinson & Berridge, 1993) and provoke craving and relapse in humans addicted to drugs (O'brien *et al.*, 1992b) and affect the maintenance and reinstatement of drug self-administration in animals (Arroyo *et al.*, 1998, Shaham *et al.*, 2003). However, rats vary considerably in the level of control exerted by reward-related cues and can be segregated according to so-called sign-trackers that readily approach the location of reward cues whereas goal trackers instead learn to approach the location of the reward itself (Flagel *et al.*, 2007, Robinson *et al.*, 2014, Tomie *et al.*, 1989). Sign-

trackers show higher breakpoints for cocaine under a progression ratio schedule and more readily reinstate drug-seeking behavior than goal-tracking rats (Fig.1) (Saunders & Robinson, 2011). They are also more impulsive on a 2-choice serial reaction time task (Lovic *et al.*, 2011) and choose cocaine over food more often than goal-trackers (Tunstall & Kearns, 2015, but see Vanhille *et al.*, 2015). Thus, sign-tracking appears to be an addiction-prone endophenotype that co-segregates with impulsivity. By contrast, contextual cues appear to exert greater effects on drug-seeking in goal-trackers than sign-trackers suggesting an additional level of specification in how discrete and contextual cues influence drug seeking and relapse (Robinson *et al.*, 2014).

Adolescence and risk taking behavior

Adolescence is a critical developmental window widely associated with drug experimentation and risk taking behavior (Casey & Jones, 2010). It is a period when young people become increasingly independent members of society where social acceptance and peers, rather than parents, become more important for day-to-day decisions (Blakemore & Robbins, 2012). Although the developmental trajectory of risk-taking behavior is controversial (Reyna & Farley, 2006) many have argued that adolescents are predisposed to risky decisions because they are hyper-responsive to rewards (Braams *et al.*, 2015) and lack the capacity for self-restraint and emotional regulation (Casey & Jones, 2010). Neurally, this may reflect the delayed and protracted maturation of cortical control systems within the prefrontal cortex relative to incentive- and stress-based sub-cortical systems (Somerville *et al.*, 2010, Spear, 2000). Such predetermined variations in neural development may contribute to heightened risk-taking and impulsivity in adolescents (Blakemore & Robbins, 2012) and the potential for drug use during this critical period causing irrevocable harm (Selemon, 2013).

Adolescence is also a critical period for social development where individuals learn to engage in dynamic and flexible relationships. Social experience during this

period has profound effects on neural and behavioral development. Thus, rats isolated from other rats during the peri-adolescence period show a heightened locomotor reactivity to novelty and behavioral sensitivity to psychostimulant drugs (Baarendse *et al.*, 2014, Fone & Porkess, 2008), as well as increased alcohol consumption (Lesscher *et al.*, 2015). This social intervention also have protracted effects on prefrontal and striatal circuits (Bianchi *et al.*, 2006, Dalley *et al.*, 2002, Hall *et al.*, 1998) consistent with evidence that social play depends on the integrity of prefrontal cortex and striatum (Van Kerkhof *et al.*, 2013).

Protective mechanisms

Studies in humans have identified a myriad of genetic and environmental mechanisms that afford **protection against** alcoholism and other drug addictions. For example, genetic variation in alcohol and aldehyde dehydrogenases, enzymes responsible for the metabolism of alcohol, prevents heavy drinking in certain Asian and Jewish groups due the rapid accumulation of the toxic metabolite acetaldehyde responsible for facial flushing, palpitations, nausea and vomiting (e.g. Neumark *et al.*, 2004). In other examples, gene variants that increase MAO function confer resilience against conduct disorder and antisocial behavior, frequent behavioral precursors to addiction (Caspi *et al.*, 2002). In many of these examples it is clear that genetic vulnerabilities depend on environmental elements for their full impact to be realised (Enoch, 2006, Johnson *et al.*, 1996, Kreek *et al.*, 2005). However, it is interesting to note that in alcoholic families where presumably many environmental features are shared, high levels of D2 receptor availability in the striatum appear to provide protection against alcoholism (Volkow *et al.*, 2006). Thus, as demonstrated recently, the balance between inherited and environmental risk and protective factors may be critical in determining whether individual siblings are susceptible or resistant to addiction (Ersche *et al.*, 2012, Volkow & Baler, 2012).

Research in animals supports the concept of resilience but relatively few studies have been carried out to investigate specific neurobiological mechanisms. Some notable examples include the demonstration that social defeat stress reinstates cocaine preference in wild-type mice but not in mice selectively deleted of the alpha isoform of the p38 mitogen-activated protein kinase (MAPK) in serotonergic neurons of the dorsal raphé nucleus (Bruchas *et al.*, 2011). Further, in a related study, resilience was shown to result from the overexpression of the histone methyltransferase, G9a, in the NAcB, which protected mice from social defeat stress (Covington *et al.*, 2011). **More recently, optogenetic activation of NAcB medium spiny neurons, which express D2 receptors, has been shown to protect against the development of compulsive cocaine self-administration in mice (Bock *et al.*, 2013).** Other evidence suggests that cognitive intervention may be sufficient to promote resilience. Thus, in a recent study, the long-term effects of cognitive training on cocaine-seeking behavior in mice were investigated after animals were returned to their deprived housing conditions (Boivin *et al.*, 2015). During “cognitive training” mice learned to dig for cereal rewards using odors, textures, and location as cues. It was found that this form of cognitive training was sufficient to produce a long-lasting reduction in the maintenance of a conditioned place preference for cocaine. Thus, cognitive intervention may overcome adversity and deprivation and thereby promote resilience to drug-seeking behavior. In other research, with similar translatable relevance to human addiction, it was found that under specific operant settings rats naturally prefer a sweetened saccharin solution over cocaine (Lenoir *et al.*, 2007, but see Vanhille *et al.*, 2015). Remarkably, fewer than 15% of animals with extensive cocaine exposure continued to take cocaine when offered a choice. Most animals voluntarily extinguished in favour of the non-drug alternative (see also Caprioli *et al.*, 2015). This study demonstrates that the minority of rats, like humans, are vulnerable to develop drug addiction.

Specific ‘traits’ may also confer resilience to addiction. In particular the propensity to acquire and self-administer stimulant drugs appears to depend on mechanisms distinct from those underlying the shift to compulsive drug seeking and taking. Thus, in a study by Belin

and colleagues, LR and HR rats were given extended access to daily intravenous cocaine and subsequently assessed for each of the three addiction-like criteria (Belin *et al.*, 2008). Surprisingly, both groups of animals were represented in the 0 and 1crit categories (i.e. resilient to addiction) confirming that locomotor reactivity to *novelty* does not predict the vulnerability to develop cocaine addiction but rather the propensity to self-administer psychostimulant drugs (Belin *et al.*, 2008, Piazza *et al.*, 1989). Indeed this conclusion was corroborated by the finding that HR rats show a progressive decline in responding for cocaine in the presence of an alternative (saccharin) reinforcer (Vanhille *et al.*, 2015). Thus, HR rats may be a valuable phenotype to investigate the neurobiological mechanisms underlying resilience to psychostimulant drug addiction.

Concluding remarks

Addiction to psychoactive drugs causes irrevocable harm to individuals, families, communities and the wider society. Despite recognising how addictive substances produce their pleasurable or rewarding effects through selective actions in the brain, it is still unclear why only a subset of all people exposed to drugs, including alcohol, subsequently become addicted. Few would disagree though that addiction involves complex interactions between environmental and polygenic factors, escalating cycles of binge drug intake and withdrawal, and a “vulnerable” host (Kreek *et al.*, 2005, Uhl, 2006). The seeming failure of preclinical research to develop a truly effective medications for addiction reflects in part the multivariate nature of this disorder, including the often personal reasons why people abuse *particular* drugs (Khantzian, 1985, Khantzian, 1990) and the hitherto narrow focus of animal research on drug reinforcement and the brain DA systems. The challenge for future research will be to recognise that addiction is a progressive disorder and to some extent idiosyncratic. However, the research reviewed in this article, suggests that adopting a dimensional approach to define specific behavioral endophenotypes characterised in aggregate by genes, molecules, and

circuits would reveal a deeper understanding of both protective and vulnerability mechanisms in addition.

Acknowledgements: The authors acknowledge funding support from the UK Medical Research Council (grants G9536855; G0701500; G0802729), the Newton-Cambridge Trust and the Wellcome Trust (grant WT109738MA). The Behavioural and Clinical Neuroscience Institute at Cambridge University is supported by a core award from the Medical Research Council (G1000183) and Wellcome Trust (093875/Z/10/Z).

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Figure legend

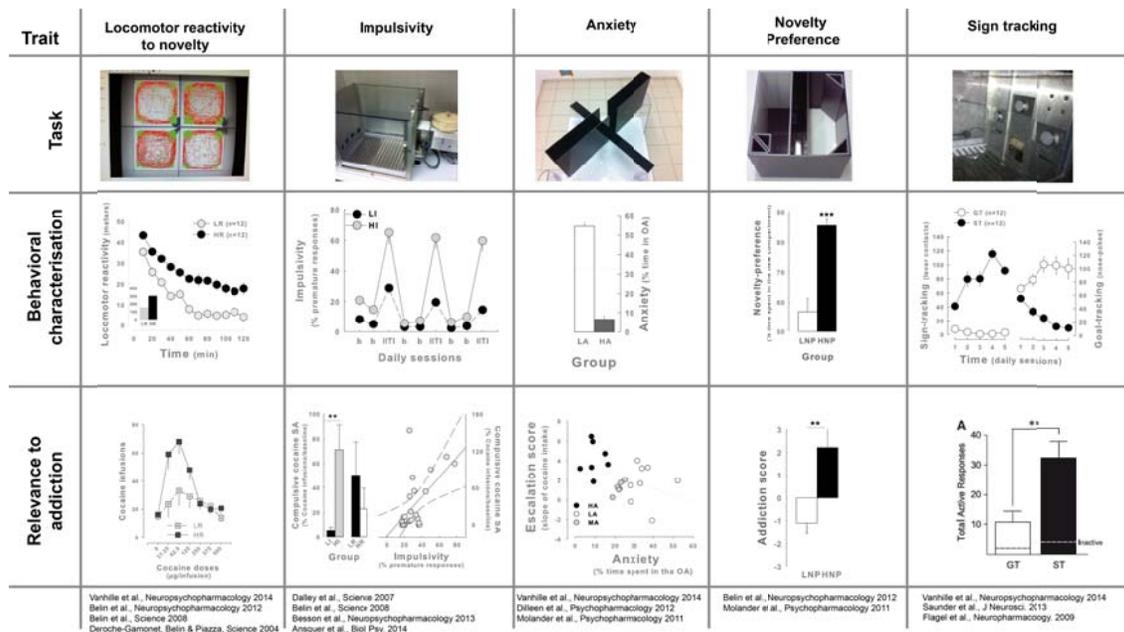


Fig.1: Relevance of distinct behavioral endophenotypes to drug-addiction-like behaviors in rats. Rats showing a high locomotor response in a novel inescapable environment (‘high responders’, HR, ‘novelty-seekers’) more readily acquire drug self-administration (SA) than ‘low responder’ (LR) rats. Highly-impulsive (HI) rats develop compulsive cocaine SA that persists despite concurrent aversive outcomes (punishment), unlike resilient HR rats. Rats selected for high anxiety (HA) on the elevated plus maze (reduced relative time on the open arms [OA] versus closed arms) show increased escalation of cocaine SA compared with low-anxious (LA) rats (MA = mid-anxious). High novelty-preferring (HNP) rats show higher ‘addiction’ scores than low novelty-preferring rats based on three criteria: (i) persistence of responding when the drug is signalled as unavailable; (ii) drug seeking despite increased response requirements; (iii) drug taking despite concurrent punishment. Rats showing increased conditioned approach responses to stimuli predictive of reward (‘sign trackers’, ST) show greater cocaine-cue evoked reinstatement compared with reward-preferring rats (‘goal-trackers’, GT). ** $p < 0.01$; * $p < 0.001$.**