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Animal Models of Drug Addiction

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1. Introduction

The study of drug addiction integrates a broad range of research fields including social sciences, psychology, psychiatry, behavioural neurosciences, pharmacology or genetics, each of which being represented in the different chapters of this book. Preclinical studies involving behaving animals have been pivotal for our increasing insights into the psychobiological substrates of addiction and so for about 100 years. Even today, our understanding and knowledge of addiction increase in parallel with the refinement of animal models of this pathology.

1.1 Necessity for animal models in drug addiction research

Whilst animal models can never reproduce the complex social and often personal reasons why people abuse drugs they nevertheless provide a rigorous means to precisely control environmental context, drug exposure as well as assessing behavioural and cognitive performance prior to drug administration. They also allow neural manipulations (e.g., using selective ligands) and so establish the causal influences of putative neural loci and, in turn, the cellular and molecular substrates, of drug addiction. Thus, to date, animal models provide a valuable means to investigate the different stages of the drug addiction cycle including especially the initiation of drug taking, the maintenance phase, which is often accompanied by binges and escalation of drug intake, and finally the switch to compulsive drug intake defined operationally by an increased motivation to take the drug, an inability to inhibit drug seeking and continued drug use despite negative or adverse consequences.

1.2 Definition and validity criteria of animal models

1.2.1 Definition of an animal model

An animal model is a preparation in one organism that allows for the study of one or several aspects of a human condition. Thus a model of drug addiction must provide insights into the neurobiological, psychological or etiological mechanisms of the pathology in humans, at least mimicking some aspects of the pathology.

Two strategies are generally used when designing animal models of drug addiction. Firstly, the model can address a specific symptom, a neurobiological or psychological feature or a behavioural / neurobiological construct associated with the pathology (figure 1).

DSM-IV diagnostic criteria for drug addiction	Psychobiological dimension	Monodimensional animal model	Polydimensional animal model
¹ Need for markedly increased amounts of a substance to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of the substance	Pharmacological tolerance		
² The presence of a characteristic withdrawal syndrome or use of a substance (or a closely related substance) to relieve or avoid withdrawal symptoms	Negative affect/mood depression, anhedonia, anxiety		
³ Persistent desire to use drugs or one or more unsuccessful efforts to cut of control substance use	Impulsivity / compulsivity behavioural control failure	Reinstatement [1-4] Relapse [5]	3-criteria model of drug addiction: inability to refrain from drug-seeking [14-16]
⁴ Substance used in larger amounts or over a longer period time than the person intended	Impulsivity / compulsivity behavioural control failure	Escalation of drug intake [6-7]	3-criteria model of drug addiction: escalation of drug intake during long access to cocaine [14-16]
⁵ Important social, occupational, or recreational activities given up or reduced because of substance use	Impulsivity / compulsivity behavioural control failure	Resistance to punishment [8] Resistance to conditioned suppression [9]	
⁶ A great deal of time spent in activities necessary to obtain, to use or to recover from the effects of substance used	Habit / compulsivity	Progressive ratio seeking-taking and second order schedule of reinforcement [10-13]	3-criteria model of drug addiction: increased break points in a progressive ratio schedule of reinforcement [14-16]
⁷ Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by continued use	Compulsivity	Resistance to punishment [8] Resistance to conditioned suppression [9]	3-criteria model of drug addiction: resistance to punishment or adverse consequences [14-16]

Fig. 1. Animal models of drug addiction in reference to the DSM IV diagnostic criteria for drug addiction (adapted from the DSM-IV [97])

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These models have been widely developed the last 40 years and have provided substantial informations about the molecular targets of addictive drugs as well as the neurobiological and psychological adaptations resulting from either acute or chronic drug exposure. Indeed, models that focus on defined features of drug addiction provide a powerful heuristic framework for determining the brain mechanisms underlying the pathology. However, they rarely address other clinical dimensions of the disorder such as behavioural predictive factors or interactions between different symptoms of the pathology. Thus, the second type of models are those that try to incorporate several symptoms of the pathology in humans, thereby providing powerful tools for longitudinal studies or even testing pharmacological treatments, but are somewhat limited in the identification of underlying mechanisms. Indeed, the behavioural complexity of these models makes it difficult to implement causal investigative studies where the end-point is well defined. We discuss the general utility and application of both modelling approaches as complementary tools to investigate the neurobiological and psychological mechanisms of drug addiction and its vulnerability.

1.2.2 Validity criteria of animal models

The validation of animal models of addiction is based upon the same principles that have been established for models in general, namely fulfilling standard criteria amongst which reliability and predictive validity are the most important [1]. However, there are other criteria that have been used widely in validating animal models of drug addiction, including face validity and construct validity [1]. Briefly, reliability refers to the consistency and stability with which the independent and the dependent variables are measured. Thus a reliable model of drug addiction must allow for a precise and reproducible manipulation of the independent variable and an objective and reproducible measure of the dependent variable in standard conditions. A further key criterion for the validation of an animal model is its predictive validity. A valid animal model should predict either the therapeutical potential of a compound in humans (pharmacological isomorphism) or a variable that may influence both the dependent variable of the model and the process under investigation in humans.

Face validity refers to the similarities between the dependent variable of the model, i.e., behaviour in the case of drug addiction, and the human condition, i.e. the symptoms of the pathology. Thus face validity may be important in designing the model but is unlikely an objective criterion to actually assess its validity. Indeed, it is very difficult, if not impossible, to provide an objective criterion to evaluate the similarities between the behavioural output of a rat preparation and drug addiction in humans when the behavioural repertoire of the two species is so different.

Construct validity has been increasingly considered in animal models of drug addiction. It refers to the ability of a model to take into account psychological or neurobiological constructs that characterise the specific pathological processes in humans. Thus, incentive sensitisation, habit formation or top-down prefrontal executive control failure are examples of constructs which have been investigated in animal models.

2. Reinforcing effects of drugs of abuse, abuse liability

As previously mentioned all addictive substances show reinforcing properties in animals. Indeed, the abuse liability of a substance is often measured by its ability to support self-

administration and a conditioned place preference [2]. In this section are reviewed the experimental designs that have been developed to investigate the reinforcing properties of addictive drugs. These procedures, combined with molecular biology and pharmacology, have been crucial in the identification and functional characterisation of the molecular targets of addictive drugs.

The seminal discovery by Olds and Milner of intra-cranial self-stimulation (ICSS) in 1954 marked a major turning point for research on the neural mechanisms of addiction [3]. The discovery that dopaminergic projections from the ventral tegmental area (VTA) to limbic cortico-striatal structures (nucleus accumbens, Acb), olfactory tubercle, amygdala, orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC) were effective substrates for ICSS sparked considerable interest in the brain dopamine systems as neural substrates for the rewarding properties of both natural [food] and drug reinforcers. A few years later Weeks developed an operant procedure to deliver intravenous morphine infusions to relatively unrestrained rats [4], a method still widely used in many pre-clinical research laboratories today. That research continued on the opioid drugs morphine and heroin for some considerable time thereafter was no surprise given the strong emphasis at that time in the DSM-III on the symptomatology of opioid dependence and withdrawal [5].

Since then it has been established that addictive substances exert powerful effects on primary and secondary (i.e. conditioned) reinforcement mechanisms. As instrumental reinforcers they strongly encourage behaviours that lead to the availability of a drug, a process subserved by stimulus-response associative mechanisms (instrumental conditioning). Abused drugs also facilitate Pavlovian conditioning whereby previously neutral stimuli in the environment become conditioned to the drug, and can predict it, or even act as conditioned reinforcers.

In operational terms, a reinforcer is a stimulus that increases the probability of a response consequent upon its presentation. Thus, all addictive drugs are reinforcers since they are self-administered by animals and humans and support conditioned place preference (a form of contextual Pavlovian conditioning). Pavlovian conditioned stimuli can act as conditioned reinforcers when presented contingently. Then they can have powerful motivational effects and support long sequences of instrumental drug-seeking behaviour by bridging delays to future drug reinforcement [6-8].

2.1 Conditioned place preference

Conditioned place preference (CPP), has been used extensively to probe the psychological [9] and neurobiological [10-11] mechanisms underlying the rewarding properties of addictive drugs [10;12], as well as negative emotional states associated with drug withdrawal [13-15]. Indeed, through Pavlovian conditioning, the negative affective state caused by drug withdrawal can induce a reliable conditioned place aversion [13-15].

The first study based on the modern paradigm of CPP was reported by Rossi and Reid in 1976 [16] although earlier demonstration of preference for a drug paired environment was published as early as the 1940's [10]. In this procedure two different unconditioned stimuli (US) are paired with two distinct environments. These contextual cues differ in their spatial configuration, colour, flooring, and sometimes even olfactory cues. Briefly, the CPP procedure involves injecting animals with either the drug in question or a control solution,

each being administered in a different environment often over successive days. The conditioning phase may combine several pairings, ideally according to a Latin square and unbiased design such that every pairing does not predict subsequent pairings, and that any spontaneous bias or preference for a compartment is initially controlled for. CPP is then tested during a drug-free choice phase where subjects are given access to both compartments. Preference for the drug-paired environment is indicative of the rewarding properties of the drug. CPP can be established not only for addictive drugs but also for natural rewards such as food, water, sexual partner and novelty [10]. Based on a plethora of studies, it is widely accepted that increased dopamine transmission is necessary for the establishment of CPP [17]. Although some authors suggest that CPP is a model of drug seeking behaviour [or drug craving], being essentially dependent upon Pavlovian associations, CPP alone cannot account for the instrumental nature of drug seeking and drug taking behaviour, which is perhaps better modelled by drug self-administration procedures.

2.2 Drug self-administration models

Drug self-administration procedures lie at the core of the most sophisticated preclinical models of drug addiction that have been developed over the last twenty years, ranging from relapse to drug taking [18-20], to loss of control over intake [21-22], compulsive drug taking [23-25] and addiction-like behaviour [8;26-28].

Addictive drugs act as reinforcers, in that they increase the probability of a behavioural response that leads to their presentation, through instrumental conditioning. Thus, animals can readily detect the contingency between an instrumental response and the delivery of a particular drug (e.g., an intravenous infusion of heroin, cocaine, nicotine or THC, or a small volume of alcohol in a magazine) and respond in an instrumental manner to obtain such drugs. The acquisition of drug self-administration is a behavioural marker of its reinforcing properties and abuse liability [2]. Indeed, apart from LSD, all drugs abused by human are self-administered by animals.

Drugs of abuse can be self-administered by a variety of routes across preclinical models, including intramuscular, intranasal, oral, and intravenous [29].

Drug self-administration was initially developed in non human primates, however since the pioneering work of Weeks (1962), rats have extensively been used to investigate the psychological, neural and cellular mechanisms underlying drug self-administration.

Self-administration procedures can be arranged according to different schedules of reinforcement [29]. In fixed ratio schedules, the drug is delivered after the completion of a fixed number of responses by the animal, thereby providing a direct relationship between the actual response and drug delivery. By contrast, in fixed interval schedules, the animal is trained to seek the drug for prolonged periods of time.

Different schedules allow for the investigation of different processes of drug taking or drug seeking behaviour which are beyond the scope of this chapter. However, insightful descriptions of, and discussions about, these schedules can be found in [6;29-32].

The acquisition of drug self-administration is widely considered to depend on the functional integrity of the olfactory tubercle and the shell of the nucleus accumbens (AcbS) [7]. An

important role for mesolimbic dopamine in this process was inferred by findings in freely moving rats that dopamine concentration is greatly increased in the striatum, and especially the Acb, following the self-administration of drugs commonly abused by humans [33]. This important study supported the influential hypothesis at that time that addictive drugs exert their primary reinforcing effects and addictive properties through activation of the mesolimbic dopamine system [34-37]. Although it is now clear that increased dopamine release in the Acb does not provide a sufficient account for the addictive properties of drugs such as cocaine, alcohol and heroin, dopamine still remains one of the most important neurotransmitters in the aetiology and pathophysiology of drug addiction, a role underscored by its proposed involvement in salience detection and learning [7;38-52].

In its classic form, the drug self-administration paradigm has provided valuable insights into the brain substrates mediating drug taking behaviour, which differ somewhat according to the particular drug under investigation [53-56]. Addictive drugs not only influence the function of the mesolimbic dopamine system [33] they also trigger a variety of between-systems anatomical [57-62] and functional neuroadaptations [63-66] as well as changes in gene transcription and function in a number of brain systems including the hypothalamus [67], the VTA [68], the amygdala [69-74], Acb [75-79], dorsal striatum [80], orbital [81-82] and prefrontal cortices [83-85], with important effects on stress responsivity [86-88] and epigenetic processes in the limbic system [77;89-92].

However, even though these data have increased our knowledge about the neurobiological substrates of the reinforcing effects of addictive drugs and the neurobiological adaptations to drug self-administration, they provide only limited insights into the neurobiology of drug addiction. As very well brought to remembrance by Serge Ahmed [93], intravenous (intrajugular) self-administration of saline had been demonstrated in water-deprived monkeys [94] a year before the pioneer morphine self-administration work in rats of Weeks (1962), thereby demonstrating that drug self-administration is a measure of instrumental conditioning, but not really a model of drug addiction.

Thus, when one considers working on drug addiction one has to keep in mind that studying drug taking behaviour is not a way of studying drug addiction. This was already stated long ago by Wise and Bozart [95] and quoted by Robinson & Berridge [96]: "To assert that all addictive drugs are reinforcers is to do little more than redefine the phenomenon of addiction." ... "To identify a drug as reinforcing goes no further than to identify the drug as addicting"; indeed, there is an obvious gulf between taking a drug on a social basis, as most of us often do, at least when one considers a glass of wine, and compulsively taking drugs. Nevertheless, even after the publication of the DSM-IV in 1994 [97] and the new diagnostic criteria for compulsive drug use that now form the hallmark of the clinical features of drug addiction many, if not all, of the early animal models focused on the "rewarding" properties of addictive drugs and their acute and chronic neurobiological effects.

Thus, during the last ten years pre-clinical research in drug addiction has attempted to better integrate one or more clinical features of the pathology according to the DSM-IV diagnostic criteria. New phenotypes have been identified based on craving or either reinstatement [20;98-99] or relapse to drug seeking [100], a loss of control over drug taking [21-22], habitual / compulsive cocaine seeking and taking [6;23-25;101] and inter-individual vulnerability to addiction-like behaviour [8;26-28].

3. Monodimensional animal models of addiction

3.1 Craving and relapse

Drug addicts show a high propensity to relapse, even after protracted abstinence [102]. This hallmark feature of addiction can be modelled in animals using two main procedures: extinction-reinstatement, initially developed by Stewart and colleagues [18-19] and abstinence-relapse [103]. Reinstatement of responding for drug can be induced by stress, low doses of the drug itself and by the presentation of drug-associated cues [20;104-112]. In the extinction-reinstatement procedure [18-19], animals experience a series of extinction sessions following a short period of drug self-administration, leading to a progressive decline in responding. Following extinction, responding for drug is reinstated by a stressful stimulus, a priming injection of drug, a presentation of a conditioned stimulus (CS) or by placing the animal in a drug-associated environment.

Reinstatement of drug seeking depends upon a broad neurobiological network which subsets are recruited based on the nature of the trigger of reinstatement, be it stress, the drug or drug associated cues and context [105]. Overall, reinstatement to drug seeking depends upon the extended amygdala, prefrontal cortex and dopaminergic neurons [105;113-114]. A large impetus has recently been put on the prominent role of glutamate homeostasis in reinstatement to drug seeking, especially focusing on prefrontal – accumbens pathways [111;115-116].

Interestingly, it has been shown that levels of reinstatement induced by contingent presentations of drug-associated cues increase with prolonged time of withdrawal. This observation suggests that drug craving increases with withdrawal duration [117-118], an adaptation that was specifically related to increase dopamine transporter (DAT) and N-Methyl-D-Aspartate receptor 1 (NMDA R1) protein levels in respectively the prefrontal cortex and the mesolimbic system [118]. However, incubation process has also been reported for food and fear, thereby suggesting that it is a common neurobehavioural adaptation to cessation of stimulation, whatever the nature of the unconditioned stimulus, rather than a specific neurobiological substrate of drug addiction.

In the abstinence-relapse procedure [103], animals are given a forced abstinence period after a brief period of drug self-administration. They are then maintained in their home cage until they are exposed again to the self-administration chamber where they are tested under extinction.

Whereas the reinstatement procedure clearly involves the Acb and both its dopaminergic and glutamatergic inputs, relapse to drug seeking depends upon the dorsolateral striatum [100;103]. Thereby, this neurobiological dissociation suggests that parallel, not necessarily mutually exclusive, neurobiological systems are involved in relapse to drug seeking. However, their respective contribution to the human craving and relapse situation remains unclear, especially the one of reinstatement since the situation in which human addicts go through extinction before responding to drug-associated stimuli or stress is very unfrequent.

3.2 Escalation of drug taking

The first well-established animal model of loss of control over drug intake, namely escalation of drug self-administration, is based on the fourth diagnostic criterion of drug addiction and was developed by Serge Ahmed and George Koob in 1998 for cocaine [21]

and 2000 for heroin [22]. Short access (“ShA”) to addictive drugs generally results in stable levels of self-administration such that plasma drug levels are controlled within an optimal level of reinforcement [119]. As mentioned previously, this pattern of self-administration does not account for the clinical features of drug addiction in humans. Ahmed and Koob thus gave extended access to cocaine to a group of animals (“LgA”, or long access) following a period of moderate exposure (ShA, fixed ratio 1, one hour a day). A second group of rats received short access to cocaine throughout the experiment.

Introduction of the long access was immediately associated with higher drug intake, as compared to ShA rats. In other words, the LgA rats escalated their rate of cocaine self-administration compared with ShA rats, which maintained a constant level of cocaine intake. LgA rats also exhibited higher rates of cocaine self-administration during the first hour of each session. Escalation of cocaine intake has been associated with an upward shift in the intracranial self-administration threshold (ICSS), indicative of reward dysfunction [21] that has been postulated by the hedonic allostasis theory [2;86-88]. However, escalation of cocaine self-administration is not associated with psychomotor sensitisation but, instead, with a sensitization of the incentive motivational properties of cocaine [120], thereby suggesting a dissociation between loss of control over drug intake and behavioural sensitisation.

Escalation of drug intake has also been associated with higher resistance to shock-induced suppression of drug self-administration and conditioned suppression [24;121], and therefore might contribute to the instantiation of addiction.

However, all rats subjected to extended access to heroin do not necessarily escalate their intake [122]. Thus, when the upper and lower quartile of a population of Lister-Hooded rats are selected on the basis of the escalation slope (a direct measure of the magnitude of escalation of drug intake over time), marked differences can be observed [122]. Whereas low escalation (LE) rats show a marked increase in their intake when extended access is introduced and then reach a plateau in their daily drug intake, high escalation (HE) rats tend to show a slower adaptation to extended access, in that they do not increase their intake as quickly as LE rats, but progressively lose control over heroin self-administration (figure 2). This first formal description of inter-individual differences in the propensity to escalate heroin intake lead to the investigation of the behavioural markers of loss of control over heroin and cocaine intake (see “Vulnerabilities to drug addiction” section). This observation may resonate well with the demonstration that escalation of drug intake does not necessarily render rats insensitive to alternative reinforcers, i.e., despite escalation of cocaine self-administration rats have been reported to prefer a saccharine solution when given the choice between this reinforcer and the drug [123]. This suggests that schedule-induced escalation of drug intake, when considered without the individual dimension, does capture one criterion of drug addiction, namely, drug is used in larger amounts, but not necessarily extends to other criteria. However, inter-individual differences can also be observed in the resistance to alternative reinforcers after extended access to cocaine [93].

3.3 Animal models of drug seeking: The distinction between drug seeking and drug taking behaviour: Second-order and two-link heterogeneous chained schedules of reinforcement

Drug addiction does not involve only taking drugs, drug addicts spend most of their time foraging for the drug. It is therefore vital to dissociate drug taking from drug seeking. In

trying to separate drug seeking from drug taking, schedules of reinforcement must be implemented in which operant responding for the drug during the drug seeking phase is not affected by the drug itself, i.e., so that drug seeking behaviour can be measured without interference by stimulant or sedative actions of the self-administered drug.

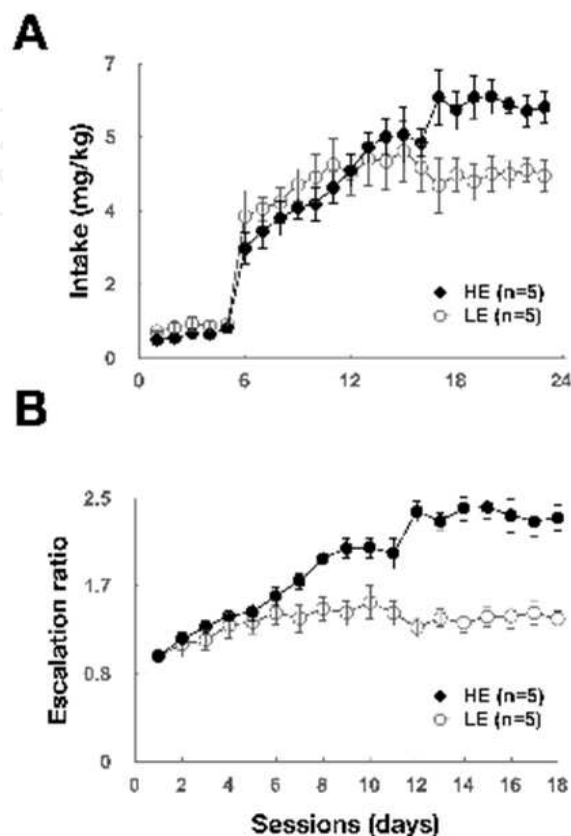


Fig. 2. Inter-individual propensity to lose control over heroin intake, after (122)

Marked inter-individual differences were revealed when the upper (high-escalation rats, HE, $n=5$) and lower quartile (low-escalation rats, LE, $n=5$) of a population of lister hooded rats were selected based on the slope of drug intake over all 18 days of the LgA phase [group: $F_{1,8} = 59.44$, $P < 0.001$]. Thus, HE and LE rats displayed a different profile both in terms of heroin intake (A) and escalation ratio (B) [group $\times$ session interaction: $F_{22,176} = 8.26$, $P < 0.001$ and $F_{16,128} = 10.20$, $P < 0.001$, respectively]. Post-hoc analysis confirmed that HE rats displayed a daily increase in both intake and escalation ratio from the 4th and 6th day of extended access, respectively (vs. LgA d1, all P s < 0.05), whereas LE rats showed no escalation at all.

Two-link heterogeneous chained schedules of reinforcement aim to dissociate spatially, temporally, and instrumentally drug seeking from drug taking behaviour. Second-order schedules of reinforcement allow the investigation of cue-controlled drug seeking over prolonged periods of time.

3.3.1 Two-link heterogeneous chain schedules of reinforcement

In this procedure completion of the first link of the chain, designated as the seeking link, results in access to the second link, or taking link, which permits, once performed, the delivery of the reinforcer. Acquisition of the chain schedule is achieved through successive steps of increasing complexity which start with introduction of the taking lever. A lever press is then

reinforced under a fixed ratio (FR) 1 schedule so that each lever press produces drug reinforcement accompanied by the withdrawal of the taking lever. After several sessions of stable responding, the seeking lever is introduced while the taking lever is retracted. The first press on the seeking lever initiates a random interval (RI) schedule with the first seeking lever press occurring after the RI has elapsed terminating the first link of the chain; this results in retraction of the seeking lever and insertion of the taking lever to initiate the second link. One press on the taking lever results in the presentation of the reinforcer followed by a time-out period. Thereafter, the seeking lever is reinserted to start the next cycle of the schedule. The effects of experimental manipulation can thus be assessed through measures of seeking responding (latency, number or response rate) as well as taking responding (latency). The interest in dissociating seeking and taking behaviour is obvious when considering that the two instrumental components are influenced by dissociable processes since they are differentially sensitive to devaluation, incentive learning or Pavlovian manipulations [124]. In addition, cocaine seeking performance is monotonically related to the dose of drug with a relatively long time out [125]. Whereas early cocaine seeking performance is profoundly affected by extinction of the taking link [126-127] but not by inactivation of the dorsolateral striatum [127], after extended training it becomes automatic, i.e., insensitive to extinction of the taking lever and sensitive to inactivation of the dorsolateral striatum [127], thereby suggesting a shift in both the psychological and neurobiological mechanisms governing drug seeking when it becomes well established [128].

3.3.2 Second-order schedule of cocaine reinforcement

In the street, drug seeking behaviour is stimulus-bond in that drug addicts forage for their drug under the control of stimuli in the environment, acting as conditioned reinforcers, that support long sequences of behaviour in the absence of the outcome. More formally, conditioned reinforcers are stimuli that have themselves acquired rewarding properties after repeated associations with unconditioned rewards. Conditioned reinforcers bridge delays between seeking and obtaining the drug. Psychostimulants, opiates, speedball, cannabis, or nicotine-associated CSs act as powerful conditioned reinforcers since they greatly enhance drug seeking behaviour when presented contingently, but not non-contingently, upon instrumental responding during, usually, interval schedules of reinforcement [6;30;32;129-130]. Conditioned reinforcers can also support the acquisition of a new instrumental response [131-132]. Such properties are clearly demonstrated in procedures where animals work to obtain presentation of a conditioned stimulus, often in the absence of the unconditioned reward.

In second-order schedules of reinforcement, the CS is presented response-contingently usually under a fixed ratio schedule, during an overall fixed interval or fixed ratio schedule for the primary reinforcer, and markedly enhances and maintains responding for long periods of time (figure 3). Thus, under a second-order schedule of reinforcement, a strong contingency exists between the instrumental response and the presentation of the CS (under a fixed ratio) as well as the relatively weaker contingency that is arranged between instrumental performance and the outcome (the drug) that is reinforced only after completion of the first ratio after each interval has elapsed. Such schedules therefore facilitate the development of stimulus-response (S-R) control over instrumental responding. In addition, it has been shown that omission of CS presentation in second-order schedules of

reinforcement disrupts cocaine seeking more than food seeking behaviour [130], suggesting that prolonged psychostimulant seeking is particularly dependent upon conditioned reinforcement.

Thus, instrumental responding during the first interval of a second-order schedule of reinforcement shows face and construct validity with regards to the behavioural features of drug seeking in humans: stimulus-bound, somewhat dissociated from the unconditioned effects of the drug and long lasting.

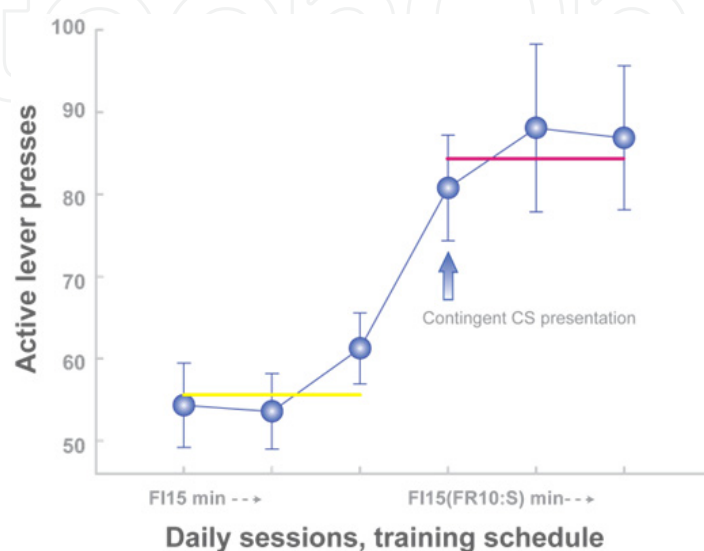


Fig. 3. Acquisition of cocaine seeking under a second-order schedule of reinforcement. Instrumental performance of a population of 24 Lister Hooded rats during the first interval of a FI15 and FI15(FR10:S) schedule of reinforcement (see text for explanation). Once animals have acquired self-administration under continuous reinforcement, the reinforcement schedule is switched to fixed intervals, with daily increments: FI1 min, FI2 min, FI4 min, FI8 min, FI10 min, and FI15 min. After 3 days of training under the FI15 schedule (*left part of the figure*), contingent presentations of the CS are introduced under a FR10 schedule such that rats are now trained under a FI15(FR10:S) second-order schedule of reinforcement. This acquisition procedure provides a direct measure of the potentiation of responding during interval schedules by the contingent presentation of the CS since they are introduced only once responding under fixed interval has stabilized. Thus, although the average response rate is 50 during the first interval of a FI15 schedule, it reaches 90-100 when the CS is contingently presented (Belin-Rauscent & Belin, unpublished).

Second-order schedules of cocaine and heroin self-administration were initially developed by Goldberg and colleagues in non human primates to assess the influence of environmental stimuli upon drug self-administration [30;129-130]. Everitt and colleagues have also established second-order schedules of drug reinforcement in rats [133]. In the study by Arroyo and colleagues (1998), rats were initially required to learn cocaine to self-administer under continuous reinforcement, i.e., FR1. After stabilisation of responding, (5 to 7 daily 2 hours sessions), a second-order schedule with fixed ratio components of the type FR_x(FR_y:S) was introduced, with initial values of x and y set to 1, so that each active lever press resulted in the presentation of the CS and the delivery of 0.25 mg of cocaine. Then x and y values were progressively increased with increments in response requirements starting with x i.e., FR5(FR1:S) and FR10(FR1:S), then y, i.e., FR10(FR2:S), FR10(FR4:S), FR10(FR7:S) and FR10(FR10:S). After stabilisation of responding under this FR10(FR10:S) schedule of

reinforcement which therefore requires 100 active lever presses and 10 one second presentations of the CS to obtain a cocaine infusion, a final fixed interval schedule FI15(FR10:S) was introduced such that a cocaine infusion was delivered only following the tenth active lever press that occurred when the 15 min interval had elapsed. Finally rats were allowed to perform cocaine seeking behaviour under this schedule for ten days. This acquisition procedure produces robust and stable CS-dependent rates of responding [133] and has been used extensively to probe the neural mechanisms involved in the acquisition, and the performance of, cue-controlled cocaine-seeking [101;134-135].

It is also possible to decrease the acquisition period to 11 days [101;136] (figure 3). In this case the training phase consists of three days of FR1 training, 2 hour daily sessions, 30 infusions (0.25 mg cocaine / infusion) followed by the introduction of interval schedules, with daily increments: FI1 min, FI2 min, FI4 min, FI 8 min, FI10 min, FI15 min. After three days of training under the FI15 schedule, contingent presentations of the CS are introduced under a FR10 schedule such that rats are now trained under a FI15(FR10:S) second-order schedule of reinforcement. This acquisition procedure provides a direct measure of the potentiation of responding during interval schedules by the contingent presentation of the CS since they are introduced only once responding under fixed interval has stabilised.

Thus, although the average response rate is 50-70 during the first interval of a FI15 schedule, it reaches 100-150 when the CS is contingently presented (figure 3), as described in several studies from Everitt's laboratory [101;137-138]. Indeed, short and long-term training under second-order schedules of reinforcement for cocaine have been very useful for investigating the neural mechanisms involved in the transition from newly acquired to well established or habitual cue-controlled cocaine seeking. Thus, acquisition of cue-controlled cocaine seeking depends upon the core of the Acb (AcbC) and its functional relationships with the basolateral amygdala [139] as well as dopamine transmission into the posterior dorsolateral striatum [137]. However, when it is well established, or habitual, cue-controlled cocaine seeking rather depends upon dopamine transmission into the dorsolateral striatum and its functional relationship with the AcbC, as demonstrated by functional disconnections between these two structures [101].

A dorsomedial to dorsolateral striatal shift in the control over drug seeking has recently been demonstrated to occur in alcohol self-administration after eight weeks of training [140a] and cocaine seeking after two weeks of training under an FI15(FR10:S) schedule of reinforcement [140b], a stage at which alcohol seeking was shown to be impervious to devaluation, i.e., was habitual. Thus addiction to both stimulants and alcohol may be dependent upon a shift from goal-directedness to habits that parallels, at the neural systems level, a progressive recruitment of the dorsolateral striatum. These data obtained in preclinical models resonate well with the recent demonstration of dorsal striatum implication cue-induced in alcohol [141] or cocaine [142] craving in humans.

3.4 Animal models of compulsive drug seeking and drug taking

As emphasised previously, addicted individuals not only consume large amounts of drugs but are also unable to repress their drug use regardless its consequences. Thus addiction shares common features with other compulsive disorders which are characterised as the uncontrollable and irresistible urge to perform an act, often to relieve anxiety or stress, but regardless of the rationality of the motivation.

The compulsive aspect of drug use in addicted subjects is even more obvious when similarities between addiction and obsessive compulsive disorder (OCD) are considered. Indeed, compulsive behaviour in the 4th version of the DSM [97] as a criterion for OCD is defined by the repetitive behaviours or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly aiming at preventing or reducing distress or some dreaded event or situation; but are either not connected to the issue or are excessive. Similarities between addiction and OCD have led, based on a modified version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS-hd) [143-144], to the development of the Obsessive Compulsive Drinking Scale (OCDS), a self-rated questionnaire which is able accurately to discriminate between alcoholic out-patients and social drinkers with high sensitivity and specificity [145], suggesting that obsessionality and compulsivity are key features of the heavily addicted individual [145].

Clinical data on abstinence from cocaine use suggest that the negative consequences directly related to use are a major reason for cessation [146]. Indeed, drug use is a high risk behaviour as it often compromised health, work and social relationships [147-148].

Preclinical models of drug addiction might therefore attempt to resemble in several respects the human conditions of compulsivity and fulfil some important features of the pathology in order to meet the necessary requirements of construct, face and predictive validity essential for the clinical application of data obtained from animal studies [1]. Of course, in animals it is extremely difficult to exactly reproduce compulsive drug seeking and taking as seen in human drug addicts because of obvious limitations including the absence of direct personal costs such as family or society problems associated with drug abuse, or limited alternative reinforcement choices.

However, despite such limitations, compulsivity in preclinical models of drug addiction should and must be defined as an inability to cease drug seeking and taking under conditions in which the drug is constantly available but its obtainment is associated with adverse consequences.

In recent years, progress has been made in an attempt to mimic human conditions of compulsive drug use.

3.4.1 Maintained drug use despite adverse consequences

1. Resistance to devaluation / adulteration

In addition to their reinforcing properties, most addictive drugs have toxic effects, which after repeated use can lead to severe health complications. Such aversive properties would normally progressively devalue any reinforcer, and facilitate the engagement of the subject in alternative responses, incompatible with the pursuit of the initial reinforcer. However, despite often acknowledging the deleterious outcome of drug use, addicts rarely achieve spontaneous voluntary abstinence, and when they manage to do so, often relapse to compulsive drug use.

Similarly, rats differentially respond to devaluation of drugs of abuse and natural reinforcers. Performance for food is markedly affected by pairing its ingestion with illness produced by injection of lithium chloride. In contrast, devaluation of orally administered alcohol and cocaine does not greatly decrease drug seeking performance [140;149-150].

Similarly, extended access to free choice between drug solutions and water interrupted by periods of withdrawal in rats results in high levels of drug intake even when solutions are adulterated with bitter tasting quinine, evidencing the compulsive pattern of alcohol drinking after protracted exposure to the drug [151-153].

2. Conditioned suppression

Until drug users explicitly experience the aversive consequences of drug use, drug taking is mainly moderated through warnings rather than actual punishment. Once experienced, aversive stimuli temporally distant from drug intake can appear, thereby rendering aversive contingencies less distinguishable. Moreover, the aversive consequences of drug use are counter-conditioned by previously extended drug presentation, which has been described as retarding the development of the conditioned emotional response [154]. All these processes may facilitate the attribution of aversive consequences to irrelevant stimuli. Adding a stimulus previously associated with an aversive outcome to the training context should normally reduce the frequency of a conditioned response. Indeed, although the aversive stimuli are not directly associated with drug use itself, a conditioned suppressor may be viewed as 'devaluing' the drug reinforcer since subjects would be required to respond for the drug in a state of conditioned fear [121].

However, Vanderschuren and Everitt (2004) found 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. These data support the view that while instrumental behaviour directed at obtaining drugs is initially a flexible, goal-directed form of behaviour, following prolonged drug exposure, drug seeking becomes insensitive to signals of punishment, thereby indicating its compulsive nature. However, it remains unclear whether in the multi-operant environment that drug addicts are normally exposed to, presentation of aversive conditioned stimuli may favour avoidance rather than abstinence.

4. Punishment

Aversive stimuli might eventually be perceived as directly associated with drug use. Punishment has often been debated as a treatment procedure, both in terms of its ethical acceptability and its efficacy. Nevertheless, it remains an undoubtedly important component of the every day life of drug addicts.

In animals, even though differing in many procedural parameters such as the locus or intensity of punishment, foot shock-induced punishment has been used in several recent models of compulsive drug seeking and drug taking behaviour. Thus we will focus here on this punisher, although foot shock-induced suppression may not easily be generalised to the human condition.

In most of the studies on drug taking despite adverse consequences, mild foot shocks, set at a constant intensity, are applied contingently upon a response reinforced by a constant dose of drug. In this case resistance to punishment is assessed through the persistence of the instrumental response despite contingent delivery of the punisher. Alternatively, the degree of response suppression is both dependent upon the magnitude of the reinforcer, the intensity of the punishment event, the schedule of their respective presentation and the delay between the instrumental responses and their consequences [155].

Consequently, Cooper et al. [156] increased daily by 0.04 mA the intensity of a shock that was initially set to 0.25 mA until rats stopped responding (lever pressing) during the 30 min daily sessions for three consecutive days. Whereas such a procedure has the advantage of assigning for each rat the final shock intensity that led to self-imposed abstinence, it constrains the opportunity for repeated testing when required.

The punishment contingency has been used at different loci of the instrumental drug taking action. Thus taking [157] or seeking behaviour [24] have been specifically punished. Since preparatory and consummatory responses have been shown to be under the influence of dissociable processes [158], it is conceivable they are differentially sensitive to punishment. In order to assess the sensitivity of seeking and taking responses to punishment Pelloux et al. used punishment in the seeking taking task that spatially and temporally dissociates the “preparatory” and “consummatory” behaviours [125]. Pelloux et al. conducted a study where either 50% of the seeking sequences were associated with the delivery of a shock instead of the activation of the taking lever or 50% of the instrumental responses on the taking lever were punished. With this probabilistic schedule of punishment both types of punishment induced a progressive suppression in performance but punishment of the taking response resulted in less suppression than punishment of the seeking response.

Finally, the efficacy of the punishment of drug seeking or taking seems to greatly depend on drug history. After short exposure to amphetamine or an opiate (remifentanyl) punishment produces robust suppression of self-administration that resumed for the opiate in all subjects approximately 5 days after punishment was discontinued [159]. However, the punishment effect obtained for amphetamine lasted much longer [157]. After extended access to cocaine, punishment produced suppression of a seeking response except in a subgroup of animals (about 25%). Thus, compulsive drug seeking appears, as in humans, only after extended exposure to the drug in a small proportion of subjects conferring on these models good predictive validity.

5. Multidimensional animal model of drug addiction: addiction-like behaviour

As previously presented, there are two main strategies when developing preclinical models of drug addiction. The first category refers to models developed to understand the psychobiological, neurological, cellular and molecular processes involved in a particular aspect of the pathology. Therefore, these models specifically address one aspect of the pathology, whether a diagnostic criterion, such as escalation of intake, resistance to punishment, high motivation for the drug, habitual instrumental performance, vulnerability to relapse, or impaired cognitive flexibility. They may also be relevant to influential theories such as behavioural sensitisation [44;96;160-161] and hedonic allostasis [2;86-88]. Such models generally assume that drug exposure triggers rather similar behavioural, neural or molecular effects in all the subjects tested.

However, these models cannot address other crucial aspects of drug addiction, such as inter-individual differences in the vulnerability to develop the pathology and their behavioural and biological correlates. They also fail to capture the multi-symptomatic nature of drug addiction. Thus, the second category of animal models of drug addiction takes into account both inter-individual differences and the complementary strategy of meeting diagnostic criteria of the pathology in humans according to the DSM-IV. Thus, to be diagnosed as

‘addicted’ an individual must fulfil three out of seven diagnostic criteria of drug addiction over the last 12 months. This approach forms the basis of a new pre-clinical animal model based on vulnerability to addiction-like behaviour in the rat [26].

In this model, three diagnostic criteria, namely [i] an inability to refrain from drug seeking, [ii] high motivation for the drug, and [iii] maintained drug use despite negative consequences, have been operationalised by, respectively, [i] drug seeking during periods when the drug is not available and signalled as so, [ii] break points during progressive ratio schedules of reinforcement, and [iii] persistence of self-administration despite punishment by contingent electric foot-shocks.

When the population is large enough, as it has been the case in several of our studies [26;28], a systematic analysis of the distributions of each of the three addiction-like behaviours revealed that the distribution of the motivation for the drug and the persistence of drug seeking ($n=40$) were best fitted by a log-normal regression (K-S: $p>0.05$, $R^2 = 0.96$ and 0.99 , respectively) (figure 4, left and middle panel). In contrast the distribution of resistance to punishment was bimodal, composed of a first log-normal distribution ($n=27$ or 67.5% of the total population, K-S: $d = 0.22451$, $p>0.1$), and a second normal sub-distribution ($n=13$ or 32.5% of the total population, K-S: $d = 0.15604$, $p>0.1$) (figure 4, right panel) which general regression fit can be described as a 3 order polynomial equation $y=3.24x^3 + 37.33x^2 + 130.86x + 146.67$ [28].

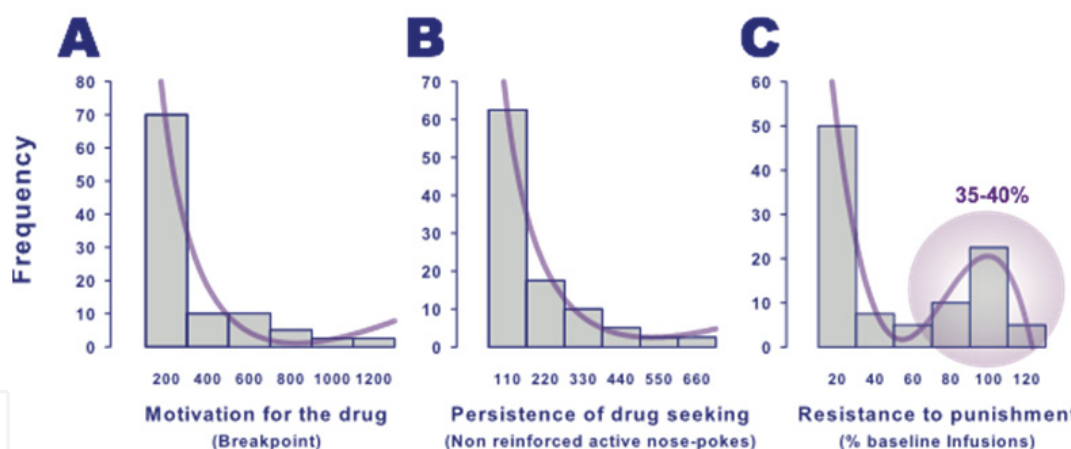


Fig. 4. Distribution of each of the addiction-like criteria, after (28)

The distribution of motivation for the drug and persistence of drug seeking (left and middle panel, respectively) ($n=40$) were best fitted by a log-normal regression (K-S: $P>0.05$). In contrast the distribution of resistance to punishment was bimodal, composed of a first log-normal distribution ($n=27$ or 67.5% of the total population, K-S: $d=0.22451$, $p>0.1$), and a second normal sub-distribution ($n=13$ or 32.5% of the total population, K-S: $d=0.15604$, $p>0.1$) (right panel) which general regression fit can be described as a 3 order polynomial equation: $y=3.24x^3+37.33x^2+130.86x+146.67$

The bimodal nature of the distribution of resistance to punishment we demonstrated in this study is in agreement with the observation of Pelloux et al. [24]. Bimodal distributions are very common in life science literature, especially during speciation process [162] whereby one whole population is somehow giving birth to two independent populations [163]. Rare in behavioural neuroscience, bimodal distributions have however been observed for drug-induced behaviours [164], suggesting that the neurobiological substrates of behavioural

inter-individual differences need in some cases to be challenged in order to reveal bimodal distribution. Our results suggest that a specific subpopulation in the rat has diverged so that it has become specifically more vulnerable to maintain drug use despite aversive consequences, as measured as resistance to punishment, when chronically exposed to the drug. This hypothesis, although speculative, when transferred to the human situation may actually resonate well with the Nesse and Berridge's suggestion that the vulnerability to drug addiction is a matter of evolution [165].

In practical terms, this bimodal distribution is particularly handy because it provides us with an objective criterion to determine a threshold in the population in order to carry out a dichotomous, categorical, strategy to identify animals that show addiction-like behaviour, i.e., 30-40% highest part of the population, depending on the study. Thus, for each of these three addiction-like criteria animals are ranked according to their score. If a rat's score is included in the 30-40% highest percentile of the distribution, this rat is considered positive for that addiction-like criterion and is given an arbitrary criterion score of 1. Then the arbitrary criteria scores for each of the three addiction-like criteria are added, and consequently four distinct groups are identified according to the number of positive scores: 0 criteria, 1 criterion, 2 criteria and 3 criteria rats (figure 5).

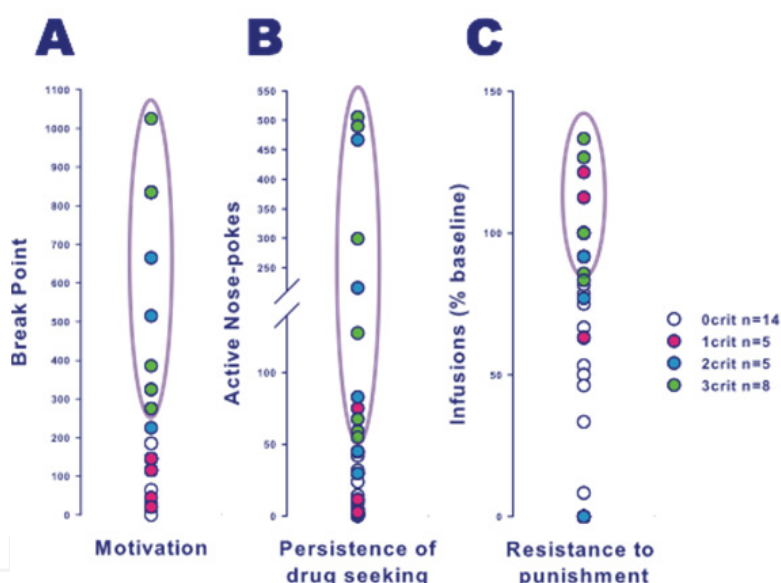


Fig. 5. Selection strategy of rats addicted (3crit rats) and rats resistant (0crit rats) to cocaine. Data analysed from (11). For each of these three addiction-like criteria animals are ranked according to their score. If a rat's score is included in the 30-40% highest percentile of the distribution, this rat is considered positive for that addiction-like criterion and is given an arbitrary criterion score of 1. Then the arbitrary criteria scores for each of the three addiction-like criteria are added, and consequently four distinct groups are identified according to the number of positive scores: 0 criteria, 1 criterion, 2 criteria and 3 criteria rats.

Behaviourally, the categorical selection is associated with a criteria-dependent magnitude in each of the addiction-like criteria (figure 6). Our model is based on the comparison of three criteria (3crit) and 0 criteria (0crit) rats. 3crit rats show high scores for each of the three addiction-like criteria and are therefore considered "addicted", whereas 0crit rats are considered resistant to addiction. 3crit rats represent approximately 20% of the population exposed to cocaine, an incidence observed in several independent studies with Lister-

Hooded or Sprague-Dawley rats as well as either nose-poke or lever press as instrumental response [26;28;101;166], that is remarkably similar to that reported in humans [167].

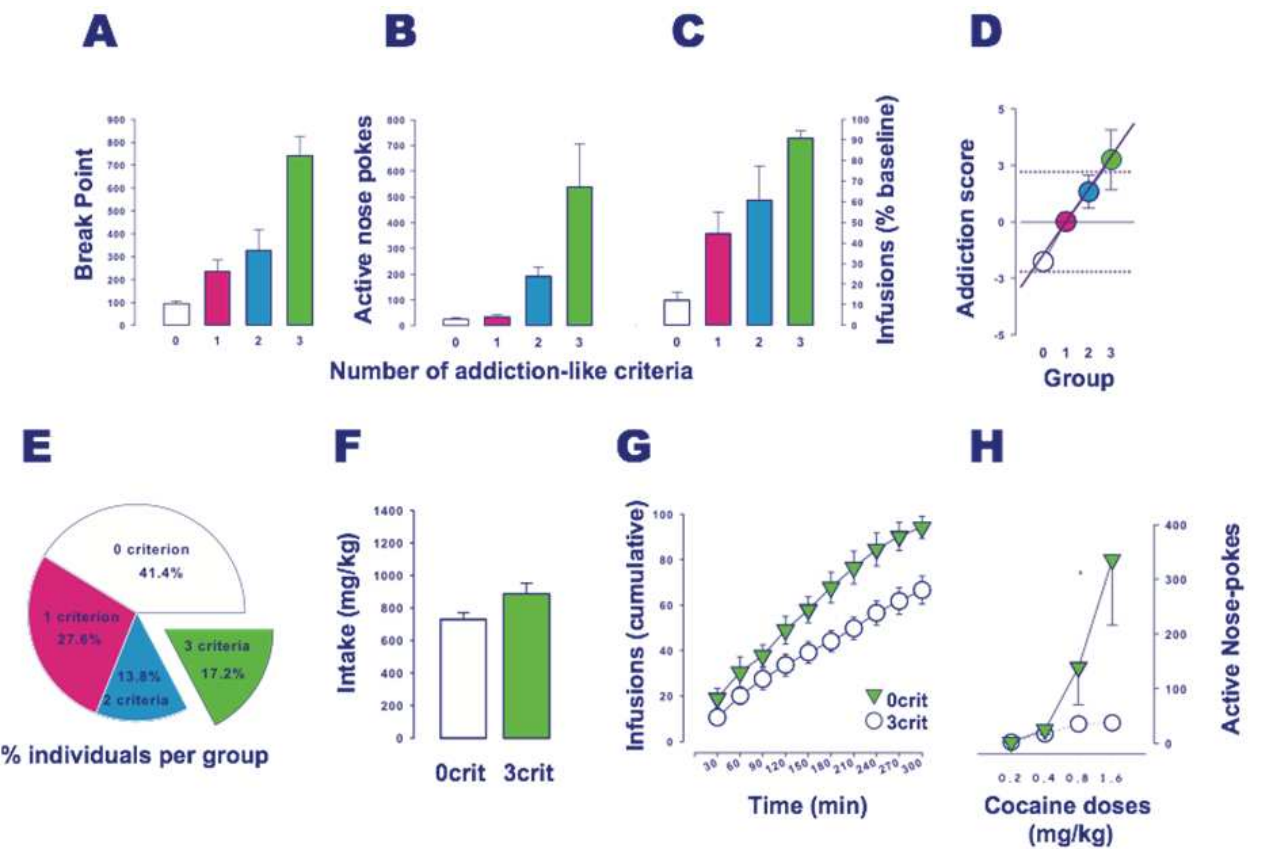


Fig. 6. Behavioural characterisation of addiction-like behaviour in the rat

A dichotomous approach to the diagnosis of addiction-like behaviour can be implemented in preclinical models of addiction on the understanding that some, but not all, animals chronically exposed to drug self-administration eventually develop one or more behavioural features resembling a clinical criterion for drug addiction as defined in the DSM-IV (see table 13.1). Thus we have operationally defined three addiction-like criteria, namely, (i) an inability to refrain from drug seeking (A), (ii) maintained drug use despite aversive consequences (B) and (iii) increased motivation to take the drug (C). Rats positive for none of the three criteria (0 criteria rats) are resistant to addiction, whereas rats that have three addiction-like criteria (3 criteria rats) are considered “addicted,” and represent 15 to 20% of the population initially exposed to cocaine (D). Importantly these behavioural differences are not attributable to differential levels of cocaine intake, since throughout protracted exposure 3 criteria and 0 criteria rats do not differ in this measure (E). Although selected on three addiction-like criteria, 3criteria rats display complementary features of drug addiction, such as inability to limit drug intake when offered extended access to cocaine (F) and high vulnerability to relapse, as measured by reinstatement of cocaine seeking behaviour by increasing doses of non contingent cocaine infusions (G). A-E: after (11), F: after (8)

Although 3crit rats do not differ significantly from 0crit rats in terms of cocaine self-administration [26;28;166], 3crit rats eventually develop higher motivation for the drug, an inability to refrain from drug-seeking, and resistance to punishment [8;26;28;101;166].

More importantly, although selected on three addiction-like behaviours, 3crit rats also display enhanced escalation of cocaine self-administration as compared to 0crit rats (figure

6F). 3crit rats therefore fulfil a fourth criterion of addiction, namely an inability to control drug intake [26] classically established after extended access to the drug [21]. This results demonstrate that loss of control over drug intake does not necessarily follow extended access to the drug, but instead develops in some vulnerable subjects exposed to cocaine self-administration for prolonged periods of time.

The predictive validity of the model is further supported by the demonstration that 3crit rats also show a high vulnerability to relapse in response to non-contingent infusions of cocaine (figure 6G) [8] or contingent presentations of a drug-associated stimulus [26]. Thus, even though selected on three addiction-like criteria, after chronic exposure to cocaine, 3crit rats display important features of clinical addiction as defined in the DSM-IV. These observations provide the model with both construct and predictive validities.

Moreover, since addiction-like behaviour emerges in three criteria rats only after extended exposure to the drug, i.e., after at least 50 daily self-administration sessions, these results highlight the importance of the interaction between a vulnerable phenotype and chronic drug exposure in the development of compulsive drug self-administration.

6. Vulnerabilities to drug addictions

Like many other psychiatric disorders, we are not all equally vulnerable to develop drug addiction. Epidemiological studies have revealed that between 15 to 35% of the population exposed to addictive drugs will develop compulsive drug use [167]. The results described in the previous section illustrate very well that inter-individual differences in vulnerability to develop compulsive cocaine self-administration can also be observed in rats. Thus, in any given population of rats exposed to cocaine only some develop addiction-like behaviour, thereby demonstrating that animal models provide a realistic estimate of risk for addiction in humans [41;166;169].

As already discussed, the underlying aetiology of the different pathways to addiction are likely to involve interactions between a vulnerable phenotype, environmental influences and drug exposure itself [170-171]. It is therefore important to identify the psychobiological substrates of vulnerability to develop compulsive drug use both in drug naive subjects and drug experienced individuals, thereby being able to develop preventive and therapeutic strategies at different stages of drug use history.

6.1 Psychobiological factors of vulnerability to drug addiction: contribution of behavioural traits

Epidemiological studies in human populations have revealed striking associations between drug use [172-173b], and certain behavioural traits [174-189] such as anxiety [190-193], impulsivity [187;194-195] and sensation-seeking [176;183;196-199]. The relevance of these traits for animal models of addiction is discussed below.

6.1.1 Anxiety

Anxiety can be assessed in preclinical models using various procedures which include the elevated plus maze (EPM) [200-201]. During the classic 5-min test session on the EPM a variety of behaviours are measured including the ratio of open and closed arms entries, time

spent in the open and closed arms, as well as self-grooming which are all indices of anxiety. High levels of anxiety including high grooming behaviour and a low percentage of time spent in the open arms of the EPM have been associated with an enhanced propensity to acquire cocaine CPP [202] as well as an increased motivation to self-administer cocaine [203], but see [204]. Trait anxiety has also been associated with an enhanced preference for alcohol [205-206], consistent with the notion that alcohol use may self-medicate underlying mood disorders related to anxiety and stress [207-208].

We have recently established that high anxiety in the EPM predicts escalation of cocaine, but not heroin self-administration in the rat (figure 7) [209].

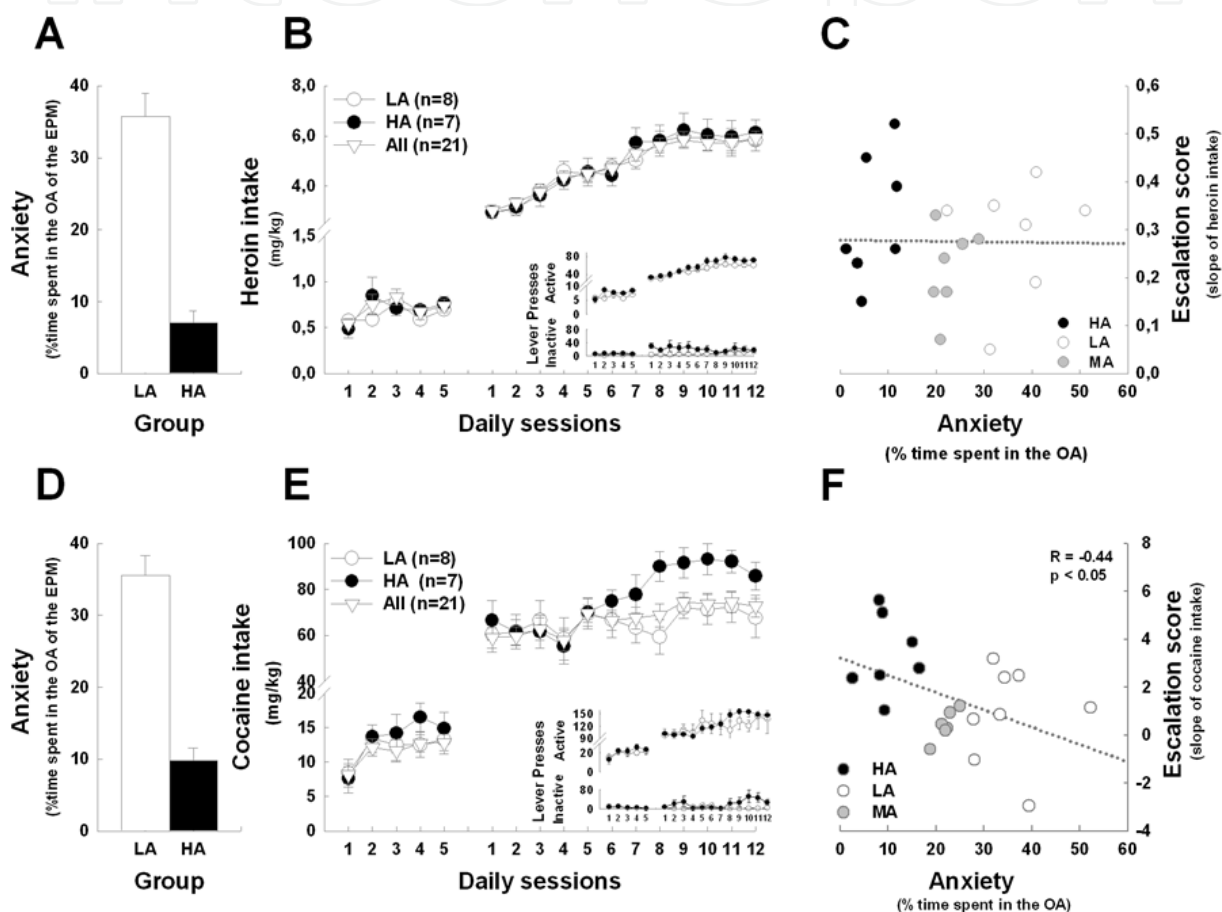


Fig. 7. High anxiety trait predicts loss of control over cocaine, but not heroin, self-administration in the rat, after (122)

High anxious (HA) and low anxious (LA) rats were selected in the upper and lower 33% of a Lister Hooded population (A & D). Whereas HA did not differ from either LA and the overall population in their escalation of heroin intake throughout 12 sessions of 6 h extended access to the drug (B) HA rats showed a marked increase in their cocaine intake as compared to LA or the overall population (E). Thus, high anxiety is related to the magnitude of cocaine escalation (F) whereas it is not related to the slope of escalation of heroin intake (C).

These data suggest that if high anxiety trait may contribute to the choice of the drug used, i.e., preference for alcohol or opiates [210], it does not necessarily contribute to the development of compulsive use when the drug is initially used as a self-medication [211]. However, the striking relationship between high anxiety levels in the EPM and subsequent

vulnerability to escalate cocaine intake suggest that high anxiety may facilitate a tolerance to anxiogenic properties of cocaine [212] perhaps because of a ceiling effect, or, instead enhance the potential anxiolytic properties of cocaine that have been suggested for low doses of the drug [213].

6.1.2 Sensation seeking / Novelty-seeking

Sensation- and novelty-seeking traits have been the focus of a large number of pre-clinical studies on addiction vulnerability (for review, see [12]).

In preclinical studies, sensation/novelty seeking trait has been suggested to be modelled both by high locomotor reactivity to a new inescapable environment (high responder phenotype, HR) [214-215], and high propensity to visit a new environment in a free-choice, novelty-induced CPP, paradigm (high novelty preferring phenotype, HNP) [12;216].

Piazza and colleagues were the first to investigate the role of sensation-seeking in this context by measuring the locomotor response of rats to an inescapable novel environment [217]. In this model, rats are placed for two hours in a new environment and their horizontal activity is monitored. Based on inter-individual differences in locomotor response animals are either selected as high (HR) or low responders (LR) according to a median division [217]. HR rats show a greater propensity to acquire psychostimulant self-administration [217] since they more readily self-administer low doses of amphetamine than LR rats [2;217]. Moreover, HR rats show a greater propensity for drug-induced neural plasticity [218-219] and increased stress-evoked dopamine release in the Acb than LR rats [220].

However, sensation seeking does not predict the acquisition of CPP for addictive drugs, which instead is predicted by novelty-seeking [12;216;221-223], the latter being a behavioural trait dissociable from the former [9;28;224].

Novelty-seeking is normally assessed by measuring the preference of rats for a novel versus familiar compartment using a procedure quite similar to CPP [225], although broad methodological differences are observed in the literature that can impact onto the nature of the behavioural construct one is investigating. Indeed, depending on the study, novelty preference has been measured as (1) the number and time duration of visits of a new arm in a Y-maze during the first 2 or 5 min, respectively, of a test session taking place 30 min after the habituation to the other two arms of the set-up [226], (2), novelty-induced place preference tested for 15 min on the third day of a protocol during which animal were exposed 30 min daily to one compartment of a CPP box [223-224] whereas locomotor reactivity to novelty has been measured in (1) circular corridors [226-227], playground maze [228] or (2) activity chambers [216;229], each environment differing from one other in terms of light intensity, openness and area.

Overall, animals selected as novelty-seekers, or novelty-preferring (HNP), are those that fall in the upper quartile range. Unlike animals selected from the lower quartile of the population, high novelty seekers readily develop a conditioned place preference to amphetamine [224;228] and self-administration of cocaine under an autoshaping procedure [230].

Thus, although both traits are dependent upon the dopaminergic system [12], they are mutually exclusive [12;216], but see [231] and therefore may predict different dimensions of vulnerability to drug addiction [12].

We have investigated the respective role of HR and HNP phenotypes in inter-individual vulnerability to switch from controlled to compulsive cocaine SA. A cohort of rats were tested for their locomotor response to inescapable novelty and, subsequently for their preference propensity to express novelty-induced CPP.

After extended cocaine self-administration these rats were tested for each of the three addiction-like criteria. Whereas LR and HR rats were highly represented in the 0 and 1crit populations, 60% of the LNP rats were included in the 0crit population as opposed to 70% of the HNP rats that showed 2 or 3 addiction-like criteria, none belonging to the 0crit population (figure 8A). This asymmetric distribution specific to LNP and HNP rats was further investigated, as illustrated in figure 8B-D which depict the representativity of LR, HR, LNP and HNP rats within the distributions for each of the addiction-like criteria. Importantly, HNP rats, as opposed to LNP rats, represented the great majority of the subpopulation resistant to punishment (figure 8D).

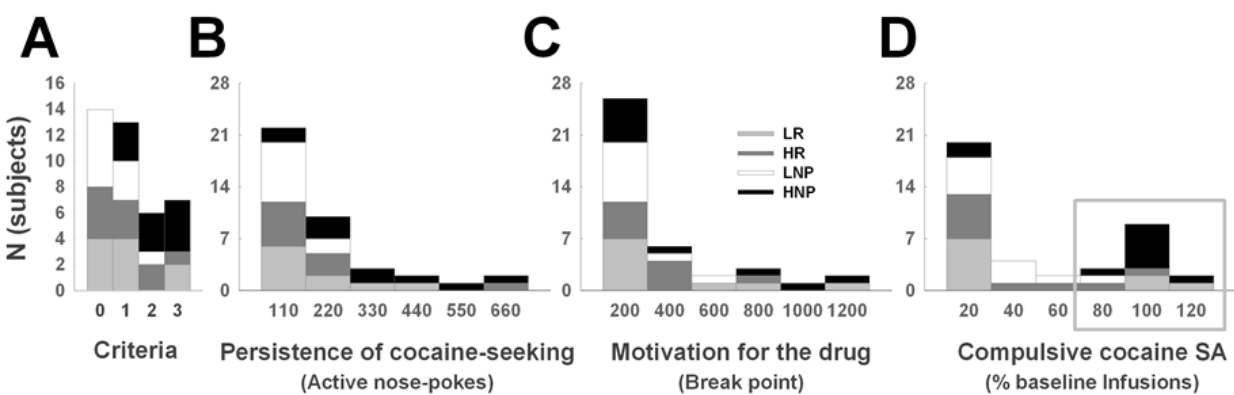


Fig. 8. High novelty preference (HNP) and sensation seekers (HR) rats are not equally distributed within the different addiction-like criteria.

A. Addiction score. The great majority of HNP rats are represented in the 2 and 3crit subgroups of the population whereas HR rats are equally distributed throughout the different groups. B-C. HNP and LNP rats are distributed asymmetrically within the population relative to persistence of drug seeking (B) and motivation for the drug (C). LNP rats are clustered on the right side of the distribution whereas HNP rats are also represented in the right part of the distribution. Such asymmetry is not observed for LR and HR rats which are equally distributed throughout the overall population for these two criteria. D. Distribution of LNP, HNP, LR and HR rats for compulsive cocaine self-administration. Whereas LR and HR rats did not show any difference in their distribution throughout the population, HNP rats were highly clustered in the compulsive subpopulation as emphasised by the encircling square. Thus HNP rats may be highly vulnerable to compulsive cocaine self-administration. Analysis of data from (28)

Thus although no differences were observed between HR and LR rats for their scores in each of their addiction-like criteria, HNP rats displayed higher scores than LNP rats in each of the addiciton-like criteria, namely resistance to punishment, inability to refrain from cocaine-seeking even if the drug is not available since they persisted, responded, more on the active nose-poke than LNP rats during “no-drug” periods and motivation for cocaine (figure 9D).

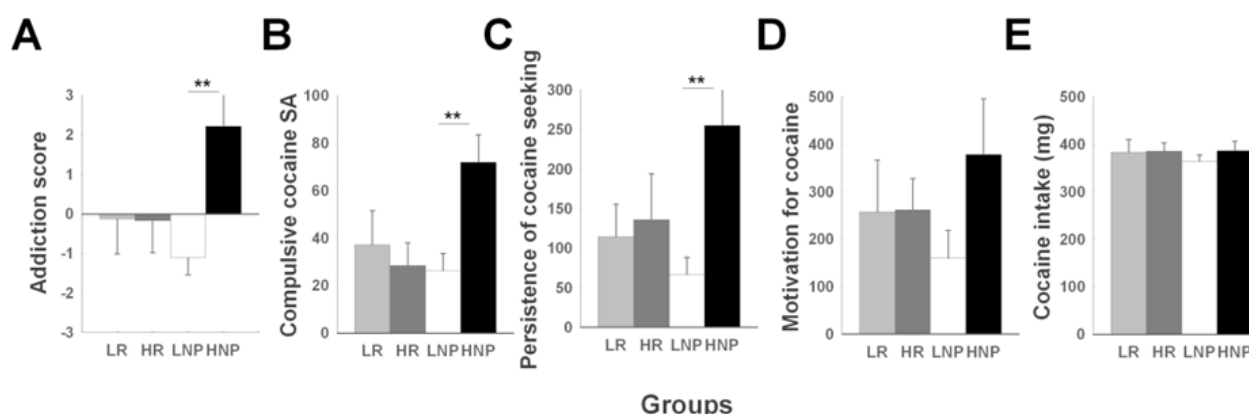


Fig. 9. Novelty Preference, but not locomotor reactivity to novelty predicts the switch to compulsive cocaine self-administration.

ANOVAs with HNP/LNP groups as between-subject factors revealed that HNP rats showed higher addiction score than LNP rats [$F_{1,18}=10.59$, $p<0.01$] (A). Compared to LNP rats, HNP rats developed compulsive cocaine SA as measured by high level of resistance to punishment [$F_{1,18}=11.16$, $p<0.01$] (B) and were unable to stop seeking cocaine when it was not available and signaled as so [$F_{1,18}=9.03$, $p<0.01$] (C). HNP rats tend to show higher motivation for cocaine than LNP though this difference did not reach statistical significance (D). These behavioral differences between HNP and LNP rats could not be attributable to differential cocaine intake since the two groups have been exposed to the same amount of cocaine throughout the experiment [$F_{1,18}<1$] (E). When compared to LR rats, HR rats showed no difference in the addiction-like behavioral measures. These two groups had behavioral scores similar to those of LNP rats, thereby illustrating that locomotor reactivity to novelty, as opposed to novelty preference, doesn't predict addiction-like behavior for cocaine.

The relationship between high novelty preference trait and vulnerability to switch to compulsive cocaine SA was further supported by a clear relationship assessed with a non parametric Spearman correlation analysis $R=0.32$, $p<0.05$, with the percentage of time spent in the new environment of the novelty-induced place preference procedure and the percentage of infusions compared to baseline when punished contingently by electric foot shocks as variables. However, no relationship was observed between locomotor reactivity to novelty and resistance to punishment (Spearman $R=-0.15$, $p=0.36$). Importantly, the behavioural differences observed between HNP and LNP rats cannot be attributed to a difference in the total amount of cocaine intake since the two groups did not differ for their total cocaine intake during the 60 days preceding the assessment of the addiction-like criteria [$F_{1,18}<1$] (figure 9E).

Since a great majority of the HNP, and none of the LNP, rats was clustered in the compulsive subpopulation, HNP rats, even though identified from a normally distributed population, may represent a specific sub-population vulnerable to compulsive cocaine intake after protracted exposure to the drug. Thereby the high novelty preference trait in the rat, as identified as the upper quartile of the population tested with the present paradigm is a promising behavioural tool for the study of the neurobiological substrates of vulnerability to compulsive cocaine intake.

While providing the first evidence for a causal relationship between novelty preference and compulsive cocaine use, this study confirms that locomotor reactivity to novelty does not predict the vulnerability to develop cocaine addiction, but does rather predict the propensity to self-administer drugs [27;217]. Altogether, these data suggest that the HR

phenotype and its underlying neurobiological mechanisms may be involved in facilitating cocaine use, but not in the transition to switch from controlled to compulsive cocaine use, the hallmark of cocaine addiction [97].

Thus two different behavioural measures suggested to reveal a putative sensation/novelty seeking trait in rats [12], namely novelty-induced locomotor activity and novelty preference, are differentially predictive of inter individual propensity to self-administer cocaine and to switch from controlled to compulsive cocaine use, respectively.

These preclinical data suggest that the correlates of the increased propensity shown by human sensation seekers to use addictive drugs [175] should be dissociated from those associated with the transition from controlled to compulsive drug use. Indeed, not only is sensation seeking a heterogeneous, multifaceted, construct [232] but it is quantified according to different, not necessarily overlapping [233], personality scales including the Zuckerman, Eysenck, Arnett and Cloninger's scales. A factorial analysis of the different items of the sensation seeking scale developed by Zuckerman [197] revealed four dimensions [234] namely Thrill and Adventure Seeking [TAS], Experience Seeking [ES], Disinhibition [Dis], and Boredom Susceptibility [BS], of which the TAS and DIS sub-scales have been suggested to refer to sensation seeking whereas the ES and BS sub-scales would refer to novelty seeking [234-235]. Further research is needed to investigate which of these sub-scales is the most predictive of the vulnerability to switch to compulsive cocaine use, thereby clearly refining the relationships between sensation seeking trait and vulnerability to cocaine addiction.

6.1.3 Impulsivity

A popular paradigm used to assess impulsivity in rodents is the 5-choice serial reaction time task (5-CSRTT), which was developed originally as an analogue of the human continuous performance task of sustained attention [236]. The 5-CSRTT requires animals to detect brief flashes of light presented pseudo-randomly in one of five holes and to make a nose-poke response in the correct spatial location in order to receive a food reward. The rat is thus required to monitor a horizontal array of apertures and to withhold from responding until the onset of the stimulus. Generally, 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 behaviour and hence a failure in impulse control [237-238]. The neural and neurochemical basis of impulsivity on the 5-CSRTT has been extensively investigated, involving important contributions from the anterior cingulate cortex (ACC), infralimbic cortex, Acb, medial striatum and by the ascending monoaminergic systems [239-240].

More recently, the 5-CSRTT has been used to screen for spontaneously high levels of impulsivity in rats, a phenotype associated with increased cocaine, sucrose and nicotine self-administration [241-243]. Interestingly, Dalley and colleagues have recently shown using microPET brain imaging that high impulsive rats have lower dopamine D2/3-binding levels in the ventral striatum as compared to low impulsive littermates [241], thereby suggesting that alteration of dopamine D2/3-receptors in the Acb may contribute to high impulsivity and vulnerability to drug addiction.

We have used the animal model of addiction-like behaviour for cocaine described in previous sections to investigate whether high impulsivity trait predicts the switch to compulsive cocaine SA.

A cohort of 40 Lister Hooded rats was screened in the 5-CSRTT for their impulse control. These rats were then tested for their locomotor response to a new, inescapable environment. Thus, prior to cocaine exposure, rats were identified as high (HI) and low (LI) impulsive or HR and LR (figure 10).

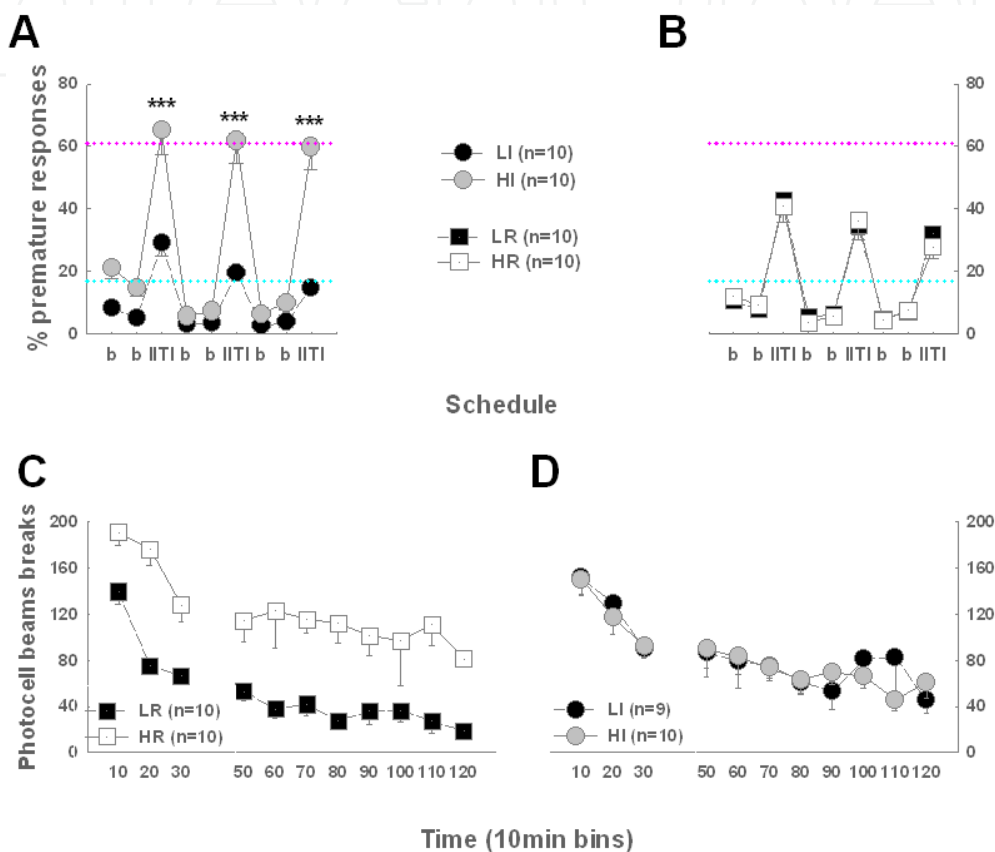


Fig. 10. Impulsivity and novelty-induced locomotor activity: two distinct phenotypes. After (27)

On two baseline days (B), premature responses in the 5-CSRTT were measured. (A and B) During long intertrial intervals (LITI), HI rats showed more premature responses than LI rats (Group: $F_{3,36} = 14.4$, $p < 0.01$; schedule: $F_{8,288} = 130.22$, $p < 0.01$; Schedule $\times$ Group: $F_{24,288} = 7.01$, $p < 0.01$) (** $p < 0.001$) (A) and HR (p<0.01) or LR rats (p<0.05) (B). HR rats did not differ from LR rats or from LI subjects (B). (C and D) HR rats were more reactive to novelty than LR rats ($F_{3,35} = 17.63$, $p < 0.01$). HI and LI subjects never differed from each other. *Comparison with HR: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (D) Pink and blue dotted lines represent the average premature responses during the last two intertrial intervals for HI and LI rats, respectively.

High impulsivity trait and locomotor response to novelty were demonstrated to be independent behavioural traits. We then tested whether high locomotor response to novelty and high impulsivity traits predicted higher propensity to acquire cocaine self-administration. We allowed animals to acquire cocaine SA with daily increasing doses of the drug. We demonstrated that HR rats acquire cocaine self-administration at doses at which

LR rats do not, thereby confirming that HR rats are more prone to acquire stimulants self-administration than LR animals [217]. However, HI rats did not differ from LI in their propensity to acquire cocaine SA (figure 11).

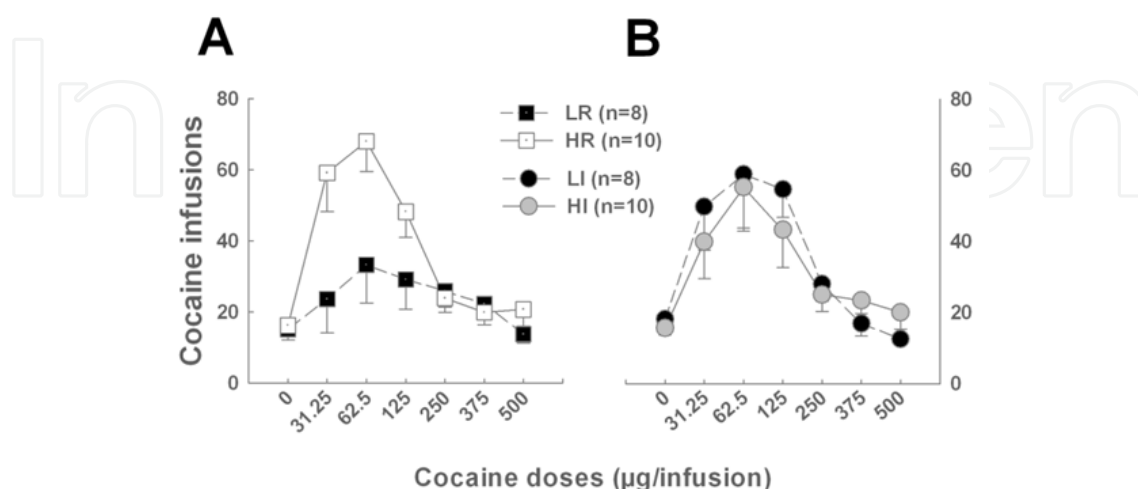


Fig. 11. Novelty-induced locomotor activity predicts the propensity to acquire cocaine self-administration, after (27)

(A) HR rats showed an upward shift of the cocaine dose-response curve compared with LR littermates (Group: $F_{1,16} = 4.9$, $p < 0.05$; Dose: $F_{6,96} = 11.73$, $p < 0.01$; Group $\times$ Dose: $F_{6,96} = 4.39$, $p < 0.01$). HR rats infused more cocaine at the lowest three doses than vehicle ($p < 0.01$). (B) HI and LI subjects did not differ in the number of self-administered cocaine infusions (Group: $F_{1,16} < 1$; Dose: $F_{6,96} = 10.79$, $p < 0.01$; Group $\times$ Dose: $F_{6,96} < 1$)

When subsequently exposed to protracted cocaine self-administration and tested for their addiction-like behaviour, rats were identified as 0, 1, 2 and 3crit rats and each animal was given an addiction score (figure 12). We then retrospectively compared HI vs LI and HR vs LR rats for their addiction score and revealed that HI rats had higher addiction score than LI whereas HR did not differ from LR rats.

This increased addiction score observed in HI rats was specifically attributed to the development of compulsive cocaine SA in these rats since they maintained cocaine SA despite punishment to the same extent as 3crit rats did. However, HR and LR rats did not differ in this behavioural criterion. The specific relationship between high impulsivity and compulsivity was further demonstrated by a correlational analysis between the percentage of premature responses in the 5-CSRTT and resistance to punishment, as assessed by a non parametric correlation analysis (figure 12).

This evidence suggests that the predisposition to initiate drug use is independent of the vulnerability to shift from controlled to compulsive drug taking, and therefore provides new insights into the various behavioural and psychological factors that influence the pathways to addiction. In particular, the demonstration that the high impulsive trait predicts the shift to compulsive drug taking behaviour is of major interest since a shift from impulse control failure to compulsivity has been suggested to play a major role in the development of drug addiction in humans [87;244] (figure 13).

Together with the demonstration that novelty preference predicts addiction-like behaviour for cocaine [28] the present data suggest that further investigations should focus on the additive or interactive contribution of high impulsivity and novelty seeking traits to the vulnerability to switch to compulsive cocaine SA.

This suggestion is timely since we [245] have recently demonstrated that high impulsive rats, as identified in the 5-CSRTT, prefer a novel compartment in a novelty-induced CPP procedure [245] (figure 14).

Thus both novelty preference and impulsivity, but not locomotor response to novelty, contribute to inter-individual propensity to switch from controlled to compulsive cocaine SA.

However, this conclusion may be taken with caution since it might be true only for stimulants. Indeed, we [122] have recently demonstrated that high impulsivity trait does not predict inter-individual differences in escalation of heroin self-administration (figure 15). This propensity was instead predicted by pharmacological flexibility in response to extended access to heroin, i.e., increased titration in response to increased availability of the drug.

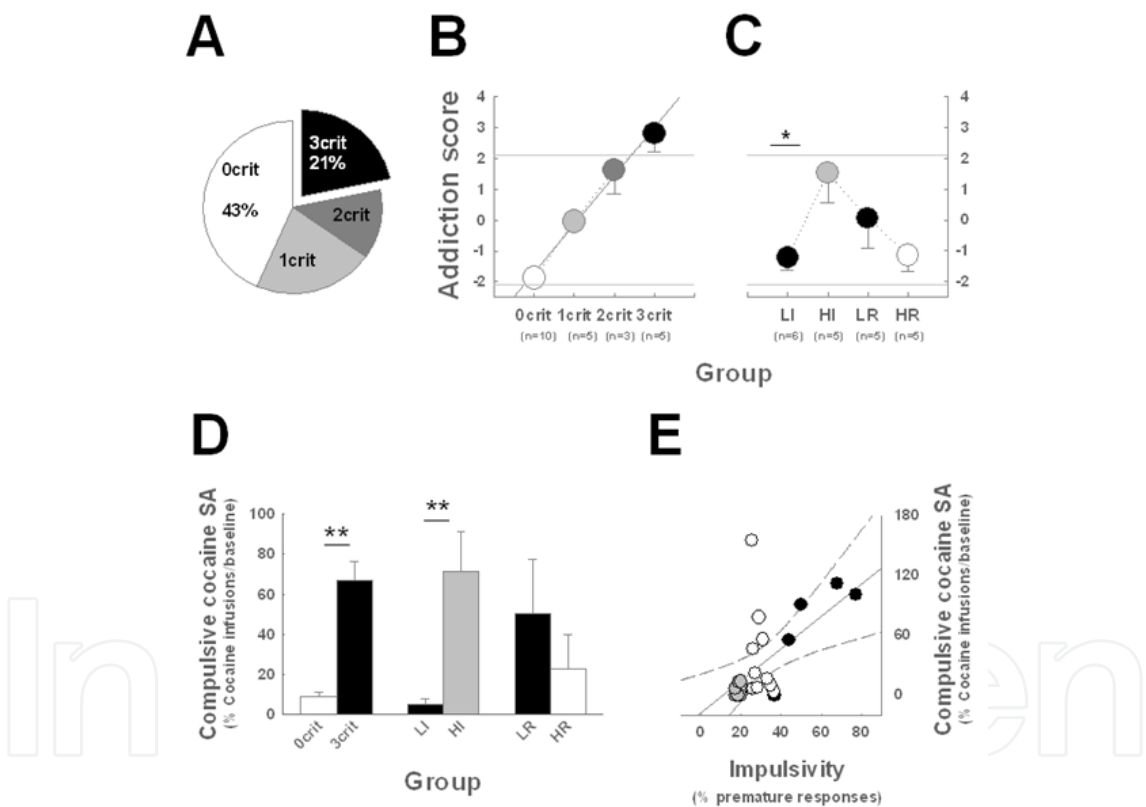


Fig. 12. Impulsivity predicts the transition to compulsivity
After extended exposure to cocaine SA 0, 1, 2 and 3crit rats were identified and were distributed similarly to previously described (A) in that 3 crit rats represented 20% of the overall population. When ranked on a linear addiction scale ($R^2 = 0.99$, Group: $F_{3,19}=34.43$, $p<0.01$), three-criteria rats had addiction scores (2.8 ± 0.6) above the standard deviation (2.1), and higher than all the other groups (B). (C) HI rats displayed higher addiction score than LI rats ($F_{1,9} = 7.55$, $*p<0.05$), whereas HR rats did not differ from LR rats. (D) HI rats ($n=5$) displayed higher resistance to punishment than LI rats ($n=6$) ($F_{1,9} = 12.79$, $p<0.01$), whereas HR ($n=5$) rats did not differ from LR rats ($n=5$). (E) Impulsivity predicts compulsive cocaine self-administration ($R = 0.42$, $p<0.05$). Gray and black shadings represent LI and HI rats, respectively.



Fig. 13. Impulsivity and compulsivity in drug addiction. It has been suggested that a shift occurs from impulsivity to compulsivity in the control over drug seeking during the development of drug addiction (left). According to this theoretical framework, drug use is initially controlled by the positive reinforcing properties of drugs. However, when addiction develops drug taking is no longer controlled by positive reinforcement but, instead, is controlled by negative reinforcement and the need to avoid the negative consequences of withdrawal. Other theoretical frameworks suggest a contribution of both impulsivity and compulsivity to different stages of the addiction cycle (right). Impulsivity might then be associated with drug taking and relapse, whereas compulsivity might be associated with craving, bingeing and insensitivity to negative feedback.

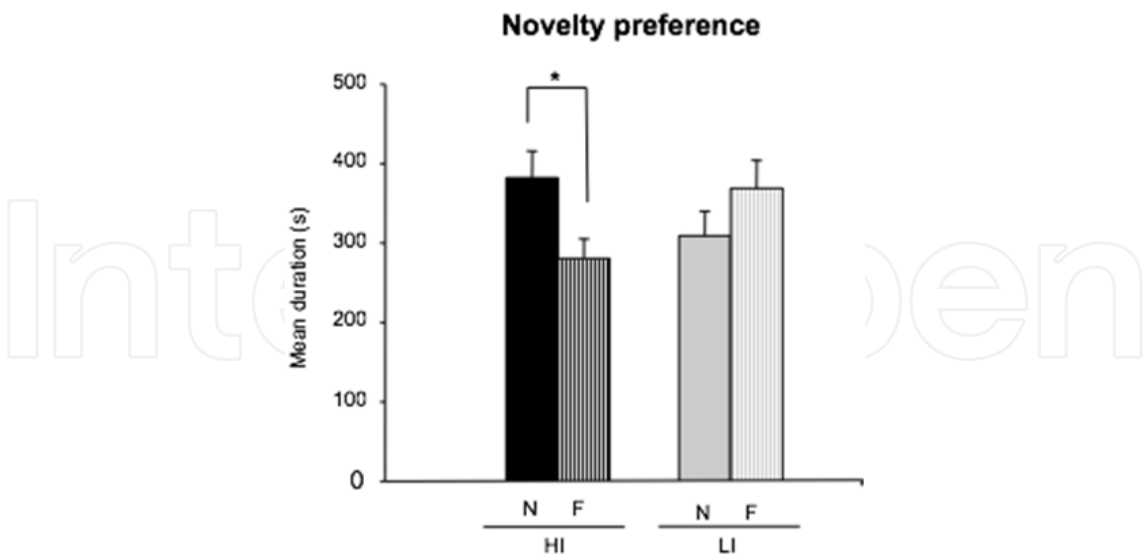


Fig. 14. High impulsive rats seek novelty HI rats explored the novel compartment of the CPP apparatus for significantly longer period of time compared with the familiar compartment, a preference that was not observed in LI rats (group x compartment interaction: $F_{1,24} = 6.53$, $p=0.017$; post hoc t-test $p=0.031$). However, there was no significant difference between HI and LI rat in the total time spent in the novel compartment. LI rats showed a trend increase in time spent in the familiar compartment compared with HI rats ($p=0.059$).

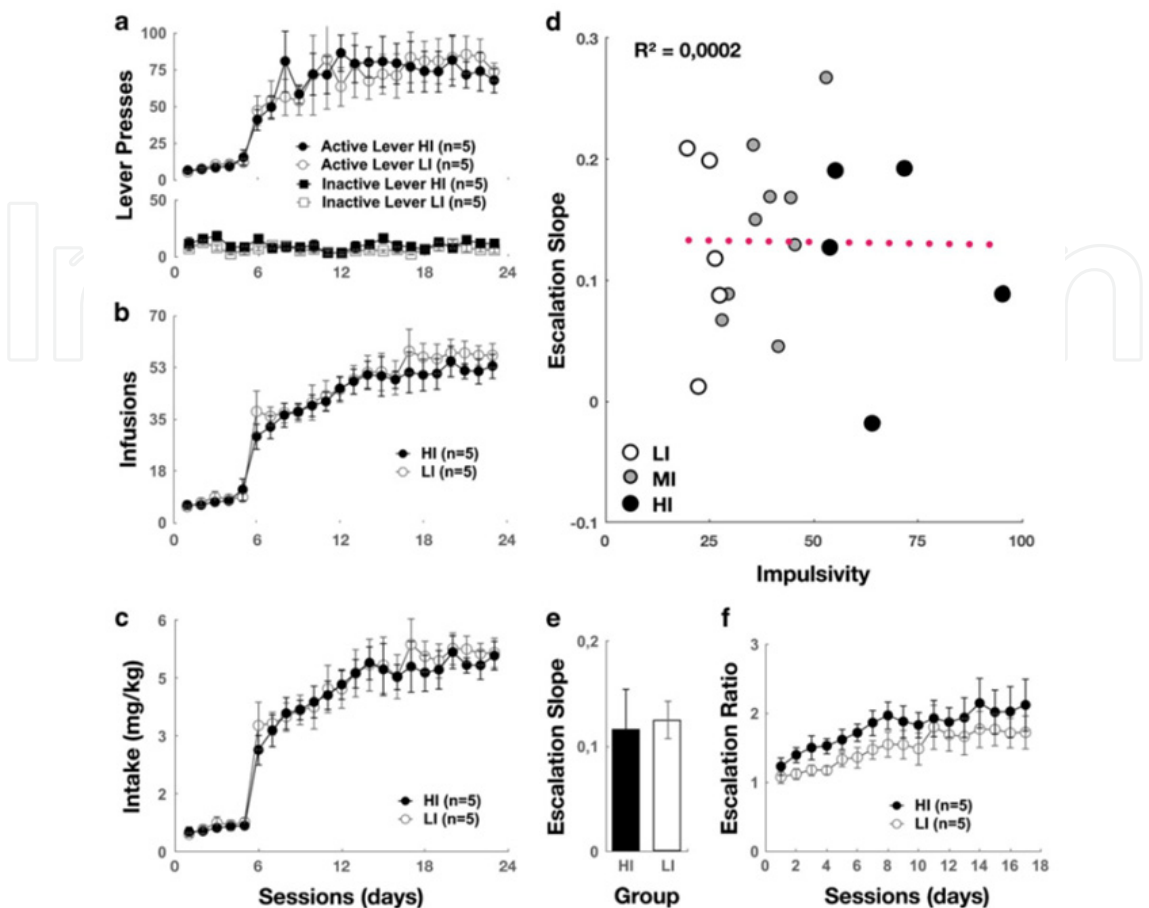


Fig. 15. High impulsivity trait does not predict a greater propensity to escalate heroin SA. After (122)

Extended access to heroin resulted in escalation of heroin SA over time in both HI and LI rats (a-d). After 5 days of 1-hour access to heroin, an 18-day 6-hour daily self-administration period was introduced. Following initiation of the LgA sessions, HI rats (n=5) and LI rats (n=5) did not differ in their time-dependent increase in active lever presses (a), heroin infusion (b), and intake (calculated as the amount of heroin self-administered by each rat in milligrammes per kilogramme body weight) (c). A dimensional analysis based on the overall population tested (n=19) did not reveal any correlation between the individual level of impulsivity (percentage of premature responses during the last two 7 s-LITI sessions) and the propensity to escalated heroin SA (escalation score; calculated as the slope of intake over 18 days od LgA for each subject) (d). Consequently, HI and LI rats differed neither in their escalation slope (e) not in the increase of their ER (intake for each LgA day divided by intake for day 1) over the 18 LgA sessions (f).

This observation is of interest since it suggests that pharmacological flexibility in response to changes in drug availability and individual propensity to titrate drug intake according to drug availability may protect against loss of control over heroin SA. Nevertheless, the marked dissociation between high impulsivity trait and individual propensity to lose control over heroin intake is in marked contrast with the demonstration that high impulsivity predicts increased vulnerability to lose control over cocaine SA [241]. Such dissociation suggests that heroin and cocaine addiction may not necessarily share common etiological factors, or, since impulsivity is a multifaceted construct [246], that other forms of impulsivity predict vulnerability to opiates addiction.

7. Conclusions

Major advances in the understanding of the neurobiological substrates of addictive drugs and their short and long-term consequences on the brain have been provided by CPP or self-administration models. Refined preclinical models, that go beyond drug reinforcement or neurobiological adaptations to repeated exposure to addictive drugs, hence with heuristic value with regards to the compulsive nature of drug seeking in drug addicts, have provided new insights into the aetiology and pathophysiology of drug addiction. Nevertheless, to date several critical behavioural aspects of drug addiction remain under-investigated, including the influence of alternative reinforcers during self-administration sessions and the role of environmental conditions, and especially environmental enrichment in inter-individual vulnerability to switch to compulsive drug use. Additionally, the recent data we have acquired on inter-individual differences in loss of control over heroin intake and the marked dissociation between high impulsivity trait and escalation of heroin SA reveal the necessity to develop preclinical models of addiction-like behaviour for other classes of drugs than stimulants. Only then will we be able to determine whether drug addiction is one pathology characterised by common etiological and pathophysiological factors or whether it should instead be considered as multifaceted, with different etiological and pathophysiological pathways, depending, at least, on the drug [56].

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