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How preclinical models evolved to resemble the diagnostic criteria of drug addiction

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Abstract

Drug addiction is a complex neuropsychiatric disorder that affects a subset of the individuals who take drugs. It is characterized by maladaptive drug-seeking habits that are maintained despite adverse consequences and intense drug craving. Despite extensive research, the pathophysiology and aetiology of addiction is only partially understood, due to the gap between current preclinical models of addiction and the clinical criteria of the disorder. Here we give a brief overview, based on selected methodologies, of how behavioral models have evolved over the last fifty years to the development of recent preclinical models of addiction that more closely mimic diagnostic criteria of addiction. These new models will hopefully increase our understanding of the complex neurobiological mechanisms whereby some individuals switch from controlled drug use to compulsive drug-seeking habits and relapse to these maladaptive habits. Additional, by paving the way to bridge the gap that exists between biobehavioral research on addiction and the human situation, these models may provide new perspectives for the development of novel and effective therapeutic strategies for drug addiction.

Drug addiction is a complex neuropsychiatric disorder that affects a subset of the individuals who use drugs [1, 2]. It is defined as a compulsive relapsing disorder characterized by maladaptive drug-seeking habits maintained despite adverse consequences [3][4]. The diagnosis of drug addiction has progressively evolved from pharmacology-related features, such as tolerance and withdrawal (in earlier versions of the DSM) to more psychological and behavioral features reflecting the compulsive nature of the disorder, namely maintained drug use despite adverse consequences, in the DSM-IV and the addition of drug craving in the DSM-5 [5].

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The modern study of the neuropsychopharmacological mechanisms of drug addiction began with the development of the rat intravenous drug self-administration (SA) procedure in 1962 [6]. This procedure is still the gold standard in the field, but as recognized some years ago, allowing rats to lever press for intravenous or oral delivery of addictive drugs for several hours per day, for a couple of weeks, falls short of modelling human addiction [7]. Additionally, despite the development in the 1970's [8-9] of reinforcement schedules that more closely mimic the complex drug-seeking behavior in humans the majority of studies use low rate fixed ratio (FR) reinforcement schedules to study mechanisms of drug reward [10-12], reinstatement after extinction [13-15] and relapse after forced abstinence periods [16-18] (**figure 1**).

Importantly, FR schedules in which animals receive a drug infusion on completion of the first ratio do not allow the investigation of the neurobiological substrates of drug seeking behavior over protracted periods of time, a key psychological characteristic of those addicted to drugs [5].

More recently, new preclinical models of addiction [19-27] with better heuristic value with regards to the clinical definition of addiction have emerged. These models are based on SA procedures that have been refined to operationalize the core psychological constructs of the disorder, namely 1) escalated drug intake [28, 29] 2) maintained drug use despite adverse consequences [21, 22] and 3) compulsive [24,26] drug seeking habits controlled by drug-associated stimuli in the environment [30] 4) that facilitate relapse after voluntary self-abstinence [23, 27, 31].

By focusing on late, but not early, stages of the addiction cycle (**figure 1**), new preclinical models of addiction may help identify the neuropharmacological and molecular mechanisms underlying the "*addiction vulnerable individual*", thereby filling the gap between clinical and preclinical research that has resulted in a failure to develop new effective treatments for addiction.

In this review, we provide an overview of how preclinical models have evolved from Pavlovian and instrumental mechanisms of drug reinforcement to recent models of addiction (for a more exhaustive discussion see [20, 32-34]). We will discuss the psychological processes on which each model stems, thereby defining their interest and limits.

Instrumental and Pavlovian mechanisms subserving drug use: drug reinforcement

Drug addicts initially take drugs because they exert powerful effects on primary and secondary (i.e. conditioned) reinforcement mechanisms [35-38]. The acquisition of SA of a drug is a behavioral marker of its reinforcing properties. SA procedures can be arranged according to different schedules of reinforcement [39], the most commonly used (**figure 1**) consisting of ten to twelve daily two hours sessions of training under FR 1 schedule [40-44], such that each lever press results in a drug infusion, often predicted by a contingent presentation of a discrete stimulus that will become a conditioned stimulus (CS) through Pavlovian conditioning.

In FR 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 so that the response rate of the animal, that remains stable over time, is determined by the unit concentration of the drug. Thus, in its classic form (FR, less than two weeks of training, **figure 1**), the drug SA procedure has provided valuable insights into the brain substrates mediating volitional drug-taking behavior [45], which differ somewhat from one drug to another [46]. Addictive drugs not only exert their reinforcing effects through activation of the mesolimbic dopamine system [47] where they hijack synaptic plasticity processes [48, 49], such as long term potentiation or long term depression [50-51], but they also trigger a variety of between-systems neuroadaptations [10, 52, 53] and changes in gene transcription and function, partly mediated by epigenetic adaptations [54-58]. These adaptations occur in a number of brain systems [10], including the nucleus accumbens [49, 55, 59], the amygdala [60], the dorsal striatum [61-65] and the prefrontal cortex [52, 66-69], with important effects on inhibitory control and stress responsivity [70, 71].

Preclinical models of relapse

Extinction-reinstatement procedure—An influential advance in the development of preclinical models of addiction is the reinstatement procedure, initially suggested to model relapse in humans [15]. Shaham and others have greatly contributed to the refinement of this broadly-used procedure, extensively reviewed elsewhere [72, 73] and in the present issue. Reinstatement of instrumental responding, following extinction training, can be triggered by stress [74], the drug itself [22, 75-77], the environmental context [15], and drug-associated CSs [78-79].

At the neurobiological level, reinstatement of instrumental responding for addictive drugs has been associated with various structures of the corticostriatal circuitry that include, but are not restricted to, the shell and core of the nucleus accumbens (AcbC) and their glutamatergic afferents from the prefrontal cortex, the basolateral amygdala (BLA), and central nucleus of the amygdala (for an exhaustive review see [15]). The neurobiological substrates of reinstatement depend upon the drug and the procedure used to reinstate the response: stress, drug priming, contextual cues, as well as CSs.

These cue-induced reinstatement procedures stem from the interaction between Pavlovian and instrumental processes [38]. They often consist of a single instrumental session performed after extensive extinction training (typically 10 to 12 sessions) following short-term drug self-administration (10 to 12 days). Thus, rats that had never been trained to seek cocaine (see following section for drug seeking procedures), but merely trained to take cocaine on a low FR schedule, are exposed to this session during which each lever press results in a contingent presentation of the drug-associated CS. Instrumental performance during a reinstatement session therefore reflects the acquisition of conditioned reinforcement [38], whereby the animal learns to lever presses for the conditioned reinforcing properties of drug-associated CSs, in the absence of the drug. Cue-induced reinstatement therefore assesses directly the motivational and reinforcing value of drug-associated stimuli.

However, abstinence in humans occurs after protracted drug use, it is often voluntary and triggered by adverse consequences and relapse is triggered by drug-related stimuli that have been extensively used by addicts as conditioned reinforcers.

Novel models of relapse: self-abstinence and relapse in the face of adverse consequences—Thus, new preclinical models of relapse have been developed [23, 27, 80] that more closely resemble voluntary abstinence and compulsive relapse. They are based on motivated abstinence in rats trained to self-administer the drug in the presence of adverse consequences, operationalized as mild footshocks over repeated sessions [23, 27, 80]. Inter-individual differences are observed in the rate of decrease of instrumental responding, reflecting the dimensional nature of compulsivity in preclinical models [77], but rats eventually stop responding for cocaine infusions or bouts of alcohol [23, 27]. Relapse to compulsive drug use is measured by the propensity to resume responding for the drug in sessions during which the punishment is not delivered.

Similarly, conflict-based models of relapse have been developed [81] to capture the conflict existing in drug addicts between resuming drug use and its associated adverse consequences. In these models, some of the rats initially trained to self-administer cocaine, that had stopped lever pressing for at least three days after an electric barrier was introduced (by electrifying the floor area near the lever), display a propensity to resume lever pressing despite punishment in response to the non-contingent presentation of cocaine-associated cues. At the neurobiological level, context-induced relapse to ethanol seeking, following punishment-induced abstinence, has been associated with an activation of neurons in the nucleus accumbens shell, projecting to the lateral hypothalamus, because an inactivation of these neurons abolished relapse [27]. Relapse in conflict-based situations was shown to be subject to inter-individual differences and was abolished in vulnerable individuals by blocking dopamine receptors in the AcbC, a structure that lies at the center of the circuitry mediating the establishment of drug-seeking habits and compulsivity (see below).

Therefore, even if they remain mostly based on only a short regimen of SA, these emerging procedures, some of which factoring in the notion of inter-individual differences, will shed light on the neural substrates of relapse following self-initiated and maintained abstinence in the face of aversive outcomes, a hallmark of the human situation.

From escalation of drug intake to addiction-like behavior: models of aberrant drug taking

Escalation of drug self-administration—By the late nineties, some groups put a large impetus on the importance of using more chronic SA procedures than those described above, in order to more closely resemble the human situation. Koob and Ahmed [28, 29] used the model of escalation of drug SA to investigate the neurobiological adaptations to chronic drug exposure under extended access, that results in a daily increase in drug intake suggested to reflect loss of control [82]. While 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 (so-called titration), the introduction of extended access to the drug (6 or 12-hour daily) results in a progressive increase in daily intake in these long access (‘LgA’) rats. This procedure is therefore highly valuable in

exposing animals to high levels of intoxication resulting in a shift of their hedonic set-point [29, 83, 84], an index of dependence [10, 85, 86]. At the neurobiological level, the escalation of heroin intake has been associated with a recruitment of the corticotropin-releasing factor [87] and kappa opioid receptors [88]. Interestingly, relapse to cocaine "seeking" after a prolonged period of abstinence, following extended access to cocaine, is associated with a persistent increase in the proportion of neurons in the AcbC that phasically fire during cocaine seeking, perhaps pointing towards the mechanisms whereby cocaine-seeking behavior in a seeking-taking task (see below) becomes compulsive [24] following exposure to extended access.

However, extended access is neither necessary nor sufficient to trigger escalation of drug intake and compulsive drug SA. Indeed, all rats provided extended access to heroin do not necessarily escalate their intake [89]. 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 particular, they do not increase their intake as quickly as LE rats in response to increased drug availability, but they progressively lose control over heroin SA. This suggests that despite high rates of drug SA, some rats do maintain control over their daily intake, whereas only a subset of the population actually escalates. This subset is characterized by a "neuropharmacological rigidity", in that their titration boundaries (or reinforcement homeostasis range), the neurobiological substrates of which remain to be identified, seem narrower than that of non-escalation rats, so that the neurobiological mechanisms controlling drug use break in the former under the pressure of extended access to the drug.

Vulnerability to lose control over drug intake may therefore stem from a lack of neuropharmacological flexibility, challenged by extended access to the drug, which, by itself, is not sufficient to trigger addiction-like behavior. Indeed, rats having developed addiction-like behavior [22] following at least seventy sessions, subsequently display an escalation of drug intake when given extended access to the drug. This suggestion that escalation of SA may be a symptomatic consequence of addiction was further confirmed by the recent evidence that rats trained in 6-hour extended daily sessions for more than 30 days escalate their intake but do not develop addiction-like behavior [90].

Addiction-like behavior—Inter-individual vulnerability to addiction-like behavior has instead been demonstrated in rats by Belin and colleagues [21, 22] by operationalizing the main clinical criteria of the DSM-IV, namely (i) increased motivation to take the drug as measured in a challenging progressive ratio, (ii) an inability to refrain from drug-seeking as measured during periods when the drug is signalled as not available, and (iii) maintained drug use despite aversive consequences as measured by maintained drug self-administration despite punishment (for more details see [20-22, 77, 91, 92]). In this model, rats positive for none of the three criteria (0 criteria rats) are resistant to addiction, whereas rats meeting the 3 addiction-like criteria (3 criteria rats) are considered 'addicted', and represent 15-20% of the population, a proportion that is similar to that observed in human populations [1]. 3 criteria rats do not differ significantly from 0 criteria rats in terms of initial rates of cocaine SA, but they eventually develop higher motivation for the drug, an inability to refrain from

drug-seeking, and resistance to punishment [21, 22, 66, 77, 92, 93]. They also show escalation of cocaine SA when given long access to the drug as well as a high vulnerability to relapse [77] that can be greatly reduced by a pre-treatment with a mGluR2/3 agonist [78], thereby confirming the contribution of glutamatergic mechanisms to drug addiction. Thus, even though selected on “only” three addiction-like criteria, after chronic exposure to cocaine, 3 criteria rats display broad features of addiction.

This model is based on the continuum of the various behavioral features of addiction, thereby allowing a dimensional approach of the factors of vulnerability to switch from controlled to compulsive drug intake. Such a multidimensional approach has yielded a better understanding of the psychological and cellular substrates of individual vulnerability to addiction. Thus, whereas high impulsivity [21], as measured in the 5-choice serial reaction time task, and high novelty preference, as measured in a novelty-induced conditioned place preference task [92], predict the switch from controlled cocaine use to addiction, high locomotor reactivity to novelty predicts an increased propensity to initiate drug self-administration [21, 94], and an increased resilience to addiction [21, 92, 95]. This suggests that the factors that contribute to the initiation of drug use may not be those that contribute to addiction, even if both cluster in drug addicts, thereby limiting the potential inferences from correlational strategies in humans.

At the neurobiological level, addicted rats are characterized by an impairment in synaptic plasticity in the ventral striatum [93] and its cortical afferent, the medial prefrontal cortex [66], suggesting that addiction, at least to cocaine, is associated with impaired fronto-striatal connectivity in rats, as it has been shown in alcoholics [96] or former heroin addicts [97]. These findings are also in agreement with a recent demonstration that altered synaptic plasticity in the prelimbic cortex supports compulsive drug-seeking behavior in rats trained in a seeking-taking task [26] (see below).

Therefore this model [21, 22, 78] has high heuristic value, even if it is far from being the ultimate preclinical model of addiction. Indeed, some laboratories have failed to implement this model [98] that is technically challenging, as it requires the maintenance of patent catheters for more than 70 days on large cohorts (at least 40 rats, the smallest cohort out of which enough addicted rats can be reliably identified). Additionally, being based on a FR schedule, this model focuses on drug-taking behavior, whereas compulsivity is as much a disorder of drug seeking as it is of drug taking.

Dissociating drug seeking from drug self-administration: a step towards the development of novel models of addiction

The study of drug-taking behavior is not sufficient to capture the many facets of addiction. Indeed, drug addiction does not only involve taking drugs, as drug addicts spend most of their time foraging for the drug over long periods of time. It is during these long periods of drug-seeking behavior, often supported, and eventually controlled by, drug-associated CSs acting as conditioned reinforcers, that the compulsive feature of addiction is expressed. Therefore, in trying to separate drug seeking from drug taking, schedules of reinforcement can be implemented in which operant responding for the drug during the drug-seeking phase is not affected by the drug itself, so that drug-seeking behavior can be measured without

interference by stimulant or sedative actions of the self-administered drug, but instead by contingent presentations of CSs [9, 99, 100].

Seeking-taking task and compulsive drug seeking behavior—Two-link heterogeneous chained schedules of reinforcement, such as those developed by Dickinson and colleagues [101, 102], aim to dissociate spatially, temporally, and instrumentally drug-seeking from drug-taking behavior. In this procedure, rats respond on a first lever, the seeking lever, under a random interval schedule of reinforcement. The first seeking lever press occurring after the RI has elapsed results in retraction of the seeking lever and insertion of the taking lever, a response on which (FR1 schedule) yields drug infusion. 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).

This procedure has been used to probe the psychological and neural substrates of early performance or habitual drug-seeking behavior [103], as well as compulsive drug seeking [24, 26, 104, 105]. Whereas early performance (10 to 15 days) of cocaine-seeking behavior is sensitive to an extinction of the taking lever [101-103], a manipulation resulting in a devaluation of the outcome of the seeking response, a hallmark of a goal-directed behavior, it becomes impervious to such manipulation after extended (40 daily sessions) training [103]. These results demonstrate that cocaine seeking becomes habitual after extended training.

At the neurobiological level, the establishment of cocaine-seeking habits depend upon the progressive recruitment of control over behavior by the dorsolateral striatum [103], the neural locus of stimulus-response processes [106, 107], which has also been shown to subserve compulsive cocaine seeking [105].

These models of compulsive cocaine-seeking behavior, such as those developed in rats in Barry Everitt's laboratory [24], are based on a probabilistic punishment of the seeking responses. Rats initially trained in the seeking-taking task are given extended access to the drug to become heavily intoxicated. They are subsequently challenged with punishment sessions during which the completion of the seeking cycle results either in the presentation of the taking lever, a press on which gives access to the drug (as described above), or a contingent presentation of a mild electric footshock. A majority of rats are not keen to take the risk of being punished following their seeking responses, and therefore progressively stop seeking cocaine. However, compulsive rats, representing a subset of the population, are likely more prone to gamble under probabilistic punishment conditions, and will eventually maintain their seeking responses, so that despite being punished in half the cycles, in every other cycle they receive a cocaine infusion. At the neurobiological level, these compulsive rats are characterized by impaired synaptic plasticity processes in the prefrontal cortex, which, if restored by optogenetic modulation of neural activity, abolishes the compulsive nature of the seeking response of these animals [26].

Despite the convergent set of results between this model and the aforementioned 3 criteria model that solely addresses compulsive intake, it is important to note that the punishment

protocols are highly different: while the former is a probabilistic punishment, the latter is a procedure whereby animals have to go through at least two shock presentations before receiving each cocaine infusion [34]. Thus, whereas one procedure may rely on risk/benefit processes allowing the animal to gamble, the other offers no unpunished access to cocaine. These differences in response and cocaine access are very likely to engage divergent psychological and neural mechanisms that remain to be elucidated.

Despite its obvious interest, the seeking-taking task does not capture all the psychological features of drug seeking behavior as displayed by addicts in whom drug-seeking behaviour, expressed over protracted periods of time, is stimulus-bound. Drug-seeking and -taking habits in those addicted to drugs are not dissociated from motivational processes, in that they are also reinforced by Pavlovian conditioned, drug-associated CSs in the environment, acting as conditioned reinforcers, supporting protracted sequences of behavior, often in the absence of the outcome.

Second-order schedules of reinforcement: protracted drug seeking under the control of drug-associated stimuli—Cue-controlled cocaine seeking has been operationalized in *second-order schedules of reinforcement* (SOR) [9, 30, 100] under which drug-seeking responses by rats during prolonged drug-free periods (classically fixed interval 15 minutes) are reinforced by contingent presentations of drug-associated CSs (upon every tenth lever press). Drug-seeking performance depends as much on the presentation of these CSs as on the drug itself, thereby suggesting that the former indeed facilitate the development of aberrant incentive habits [19, 38, 108, 109].

At the neurobiological level, a shift occurs in the control over cue-controlled drug seeking from a network involving the AcbC, its functional interactions with the basolateral amygdala and the ventral tegmental area, as well as the dorsomedial striatum (the locus of goal-directed control over behavior [110, 111]) to a network involving the AcbC and its dopamine-dependent functional interactions with the dorsolateral striatum (DLS) [112-115]. Even though the precise underlying cellular and molecular mechanisms remain unknown, the functional coupling of the AcbC and the DLS [112] supporting cocaine seeking habits depends upon the recruitment of the serial, ascending ‘spiralling’ circuitry, linking the AcbC to the DLS via the dopaminergic neurons of the substantia nigra pars compacta (SNc) [116, 117]. This aberrant functional coupling of the ventral and the dorsolateral striatum that has been recently demonstrated in former heroin addicts [97] may facilitate the transition from Pavlovian incentive influences encoded in the amygdala, and controlling the AcbC, to the habit system dependent upon dopaminergic processes in the DLS. This may provide a limbic-striatal functional highway through which drug-associated impulses triggered either by internal states (stress, interoceptive cues, or negative distress) or external stimuli can engage and support rigid drug seeking habits [19].

This pathway hijacks any potential information processing by the prefrontal cortex. It therefore raises the question of the nature of psychological processes over which prefrontal executive control is lost in addiction (see [19] for further discussion).

A preclinical model of the DSM-5, are we there yet?

Over the last ten years, a great effort has been made to develop preclinical models that separately address psychological constructs and related clinical criteria of addiction, as defined in the DSM-IV, and more recently the DSM-5. Addiction researchers should continue this endeavour by developing a next generation of models that might be inspired by those that have been discussed here. When developing new models, researchers should consider the key constructs of addiction: 1) protracted seeking responses that are 2) controlled by stimuli in the environment 3) eventually become compulsive 4) after protracted exposure to the drug 5) but only in some vulnerable individuals.

Sharing construct validity with the human condition, this next generation of preclinical models should help us uncover the pathophysiological substrates of addiction and its associated endophenotypes of vulnerability. If developed within a coherent translational approach, integrating cognitive neuroscience and refined correlational approaches in humans, such as genome-wide polymorphism analysis, these models will help identify the functional significance of specific genetic, behavioral, or cognitive correlates to the vulnerability to switch from volitional drug use to compulsive drug-seeking habits. Doing so, the next generation of preclinical models of drug addiction will provide evidence-based support for understanding the complex aetiology of addiction (which cannot be reached through human studies alone), and refine its clinical definition.

Indeed, addiction is a neuropsychiatric disorder the core pathophysiological mechanism of which remains unknown, but that is currently identify as a sum of its behavioral symptoms. However, it is not because the diagnostic of addiction is based on the summation of symptoms that we should think an understanding of its core pathophysiological mechanism could be achieved by summing up neurobiological correlates of models pertaining to independent symptoms.

Thus, the challenge for the future preclinical models of addiction is perhaps to move away from a face validity approach of independent symptoms and encapsulate psychological constructs of the disorder that can also be measured in clinical studies.

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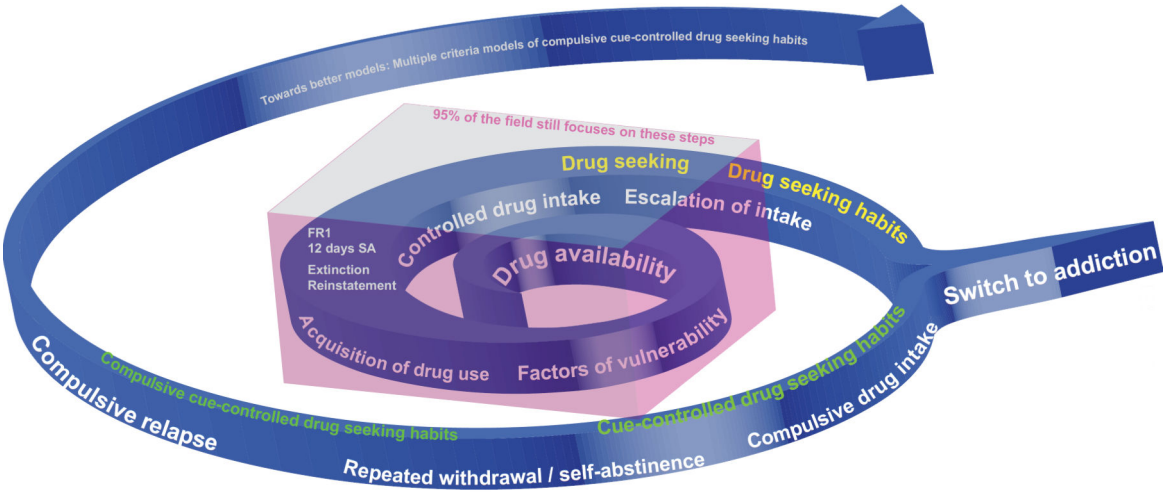

Figure 1.
The drug addiction spiral and the various ways it is investigated in preclinical research.