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Are animal models of addiction useful?

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Abstract

Background: Preclinical research involving non-human animals has made important contributions to our understanding of risk-factors for addiction, neuroadaptations that follow chronic drug exposure, and to the development of some efficacious pharmacotherapies for addiction. Despite these contributions, we argue that animal models of addiction have impeded progress in our understanding of addiction and its treatment in humans. ***Argument:*** First of all, the majority of pharmacological treatments that were initially developed using animal models have failed to prove effective for the treatment of addiction in humans, resulting in a huge waste of resources. Secondly, we demonstrate that prevailing animal models that portray addiction as a disorder of compulsion and habit cannot be reconciled with observations that psychoactive drug use in humans is a goal-directed operant behaviour that remains under the control of its consequences, even in people who are addicted. Thirdly, addiction may be a uniquely human phenomenon that is dependent on language, which necessarily limits the validity of animal models. Finally, we argue that addicted brains must be understood as one component of broader networks of symptoms and environmental and social factors that are impossible to model in laboratory animals. ***Conclusions***: A case can be made that animal models of addiction have not served us well in understanding and treating addiction in humans. It is important to reconsider some widely-held beliefs about the nature of addictive behaviour in humans that have arisen from the zeal to translate observations of laboratory animals.

Key words: Addiction; animal models; compulsion; habit; pharmacotherapy.

Preclinical addiction research includes laboratory studies with rodents and primates that characterise the individual differences that predispose to addiction and the neurobiological adaptations that occur after chronic drug exposure. Findings from these studies have made important contributions to our understanding, including risk-factors for the development of addiction (e.g. (1)), and to the identification of some novel pharmacotherapies (2). Aside from these contributions, there is scepticism about the contribution of animal models to our understanding of addiction and its treatment in humans (3). In this paper, we consider the validity of animal models of addiction and we critically review the contribution of those models to our understanding of addiction in humans and to the development of effective treatments.

What are 'animal models of addiction'?

Diagnostic criteria for substance use disorders (4) include physiological adaptations (tolerance and withdrawal), persistence of substance use despite negative consequences, increased allocation of behaviour to substance use rather than competing rewards, subjective craving, and continued substance use despite intentions to cease or reduce it. Given the diversity of diagnostic criteria, a unitary animal model of addiction is probably unattainable (5, 6). This is important in the broader context of concerns about the predictive validity of animal models of complex psychiatric disorders, which have prompted the pharmaceutical industry to drastically reduce their funding of research that relies on such models to develop novel pharmacotherapies (7). Many experimental procedures such as drug self-administration and conditioned place preference that were historically interpreted as animal models of addiction (8) are now

understood to be models of substance reward, instrumentalization, and non-addictive substance use, rather than models of addiction (5)(8)(9).

However some animal models, for example the 0/3 criteria model of cocaine addiction (2, 10) attempt to model several of the diagnostic criteria for substance use disorders (4). This model includes laboratory measures of (i) persistent drug-seeking when the drug is signalled to be not available, which is an animal model of the inability to refrain from drug-seeking; (ii) motivation to obtain the drug under a progressive ratio reinforcement schedule, which captures elevated motivation for the drug, and (iii) maintenance of drug-seeking and taking despite contingent punishment such as electric shock (also known as a 'punishment schedule'), which is an animal model of persistent drug use despite negative consequences. This and similar animal models have contributed to our understanding of the neurobiological changes that arise after chronic drug exposure and that may underlie the development of apparently compulsive and habitual drug seeking (11, 12).

Animal models have failed to deliver effective pharmacotherapies for addiction

There are many efficacious treatments for addiction (13). These include pharmacotherapies such as acamprosate and naltrexone for alcohol and opioid dependence (14, 15) nicotine replacement therapy and varenicline for smoking cessation (16), and psychological and behavioural treatments such as motivational interviewing, cognitive-behavioural therapy, and contingency management (17). When considering the contribution of animal models, it is important to distinguish predictive models (that predate human clinical research) from postdictive models, where findings from human clinical studies are back-translated to animal models (18). Some notable examples of addiction treatments that have been studied in postdictive animal models

include buprenorphine and methadone that were initially developed as analgesics (19), nicotine replacement therapy that resulted from observations that submariners switched from tobacco to snus when onboard (19), and some psychosocial treatments(20) that are adaptations of treatments for other psychological disorders (21). Our criticism of animal models focusses on predictive animal models.

Efficacious pharmacotherapies for addiction that can be at least partially attributed to predictive animal models include acamprosate, naltrexone, and varenicline (19). For example, varenicline is a partial nicotine receptor agonist that was initially tested in rodent models, where it was shown to be less reinforcing than nicotine and led to reductions in nicotine self-administration and nicotine-induced reinstatement. On the basis of these promising findings, varenicline was tested in human clinical studies where it was shown to increase abstinence and reduce nicotine withdrawal and cravings, leading to its endorsement by NICE as a smoking cessation treatment in 2007 (22). Thus, the development of varenicline as an efficacious smoking cessation treatment can be directly attributed to animal models of addiction (6, 19).

However, many other medications were initially developed in animal models, but subsequently failed to translate to clinical benefit in humans (see (18) for a review). Very few medications have been approved for the treatment of addiction in the past 20 years and those that have are only slightly better than older drugs (3, 23). For example, despite promising findings in animal models, the recently developed opioid antagonist nalmefene has trivial advantages over the older (and considerably cheaper) medication naltrexone for the treatment of alcohol use disorders in humans (24). Another example is memory reconsolidation interventions, which were advanced based on demonstrations that disruption of drug-related memories led to reductions in drug-seeking behaviour in rodents (5). However, trials of pharmacotherapies that disrupt

memory reconsolidation have not revealed clinical benefit in humans with addiction (25, 26). Similarly, D-cycloserine, a pharmacological agent that facilitates extinction of cue reactivity in animal models, does not confer clinical benefit in humans (27). Aripiprazole, another candidate pharmacotherapy for the treatment of cocaine dependence, reduced cocaine self-administration in animal models, but performed no better than placebo (28) or led to increased cocaine use (29, 30), in trials with humans.

Translational failures such as these might be brushed aside with reference to methodological issues in clinical trials, such as high placebo response rates that mask the effectiveness of a candidate treatment, poor participant engagement, or lower drug dosage in clinical trials than in animal research in order to minimize side effects (2). Our view is that these failures illustrate the inability of animal models to capture the complex nature of addiction and its treatment, and the complexity of conducting clinical trials with humans. A further objection is that, until fairly recently, animal studies of medication development used models of non-addictive drug use rather than models of addiction, which may explain why a candidate medication that had a robust effect on non-addictive drug use in laboratory animals failed to translate to clinical benefit for humans with addiction (9). The validity of this viewpoint depends on the extent to which a valid animal model of addiction is attainable, a point to which we return later.

Findings from animal models of addiction have generated a misleading picture of the nature of addictive behaviour in humans

Next, we consider the influence of animal models on conceptualisations of addiction that are widely accepted and largely unchallenged in the scientific and medical literature, and increasingly accepted by non-specialists. For example, Everitt and colleagues (12) reviewed the "burgeoning, supportive evidence" for the notion that

"drug addiction can be viewed as a transition from voluntary, recreational drug use to compulsive drug-seeking habits" (p23). Other influential theorists such as Wise and Koob (11) and Volkow, Koob & McLellan (31) also claim that addiction involves a transition to compulsive and habitual behaviour, although their explanations for the neurobiological adaptations that underlie these behavioral changes differ.

Compulsive behaviour, defined as "the maladaptive persistence of responding despite adverse consequences" (12) is modelled in animals by measuring the persistence of instrumental responding for drug despite contingent punishment such as electric shock, which is a component of the 0 / 3 criteria model (2, 10). Habitual behaviour, defined as instrumental behaviour that is independent of the value of its outcome (12), can be inferred if animals persist with instrumental responding for drug despite devaluation of the drug outcome. The aforementioned, highly influential depictions of addiction as a disorder of compulsive and habitual behaviour are largely underpinned by evidence obtained from these animal procedures (5, 12).

For present purposes, the critical question is: to what the extent can human drug-seeking behaviour be characterised as compulsive or habitual? Heather (32) summarizes several observations that clearly contradict this characterization. For example, drug use is an operant behaviour that remains sensitive to its consequences, as evidenced by the effectiveness of contingency management for the treatment of addiction (33). That is, people with addiction are able to refrain from using drugs if they receive monetary rewards (or other incentives) for doing so. Therefore, drug use is not 'compulsive' at the time it is carried out (32). Furthermore, people with addiction report high levels of problem solving in order to obtain drugs (34), rather than being the inflexible automatons that are portrayed in some of the aforementioned theoretical accounts. Demonstrations of habitual and compulsive drug-seeking that is insensitive to

its consequences in animals after chronic drug exposure cannot be consistently replicated in human addicts, in whom goal-directed control over behaviour appears to be intact (35). A broader problem for any theoretical account that depicts addiction as a compulsive disorder in which control over drug use has been lost is the observation that most people with addiction eventually recover, often in the absence of any treatment (36).

Until recently, animal models failed to consider a number of factors that have a pronounced effect on drug-seeking behaviour. As summarized by Ahmed (37): "In standard self-administration settings, animals have no choice than drug use. As a result, serious doubt exists about the interpretation of drug use in laboratory animals. Is it symptomatic of an underlying addiction state or merely an expectable response to lack of choice"? The landmark 'Rat Park' studies (38) were the first to demonstrate that morphine-exposed rats preferred plain water over morphine water if they were tested in an enriched social environment compared to if they were tested alone in their home cage. Although there are methodological weaknesses with the Rat Park studies (39), Ahmed and colleagues subsequently conducted many rigorously controlled studies that demonstrate that the majority (85-90%) of rats that rapidly escalated their drug intake when given free access to it would switch their preference from the drug to an alternative reinforcer such as saccharin if given the choice between the two (40, 41). Similarly, even 'addicted' rats (based on the 0 /3 crit model) prefer social interaction over the drug when offered the choice between them (42).

These findings raise fundamental questions about the extent to which drug seeking in 'addicted' rats is compulsive and habitual, as is commonly portrayed (11, 12, 31), rather than goal-directed and sensitive to the presence of competing rewards, as it is in humans. These findings also have implications for interpretation of the changes in

brain structure and function that are observed in laboratory animals after chronic drug exposure, and observations of comparable adaptations in humans with addiction (12, 31). As noted by Ahmed (37): "neuroadaptive changes documented in the brain of these rats should not be necessarily interpreted as evidence for addiction-specific pathological changes" (p179).

The neurobiological changes that characterize the minority (10-15%) of rats who continue to favour drugs over alternative reinforcers have recently been studied in animal models (43); these findings await replication. Furthermore, although recent animal studies that used choice tasks demonstrated that chronic drug use leads to impulsive and habitual responding and appears to disrupt goal-directed behaviour, this appears to paradoxically predispose animals to prefer the non-drug over the drug option (41, 44). This is a challenge to theoretical claims that chronic drug use causes habitual and compulsive *drug-seeking* behaviour (12).

Another recently developed animal drug self-administration paradigm also questions the importance of habitual and inflexible behaviour in the development of addiction. Building on observations of the extent of planning and problem solving reported by human addicts in order to obtain drugs (32), Singer et al. (45) developed a novel cocaine self-administration procedure that required rats to solve puzzles in order to obtain access to cocaine. The rats were required to solve different puzzles each time, which prevented drug-seeking from becoming habitual and inflexible. Nonetheless, these rats developed symptoms of addiction, similar to those captured in the 0/3 crit model. The implication is that novel drug self-administration procedures reveal findings that are fundamentally incompatible with the dogma that addiction is a disorder of compulsive and habitual drug self-administration (11, 12, 31), but rather it can involve

problem-solving and complicated sequences of behaviour, just as it does in humans (32, 35).

It is unfortunate that the broader scientific and medical community have been misled about the nature of addiction on the basis of findings from studies that used older animal models. On a more optimistic note, recent studies have demonstrated the exciting possibilities afforded by novel animal procedures that involve choices between drugs versus alternative reinforcers or social interaction, or that require problem solving rather than favour the development of habits. One might argue that we should intensify efforts to develop and validate these novel animal models, and embrace any rethink about the nature of addictive behaviour that is suggested by findings obtained from these models (18, 40, 43, 45). However, this may be misguided, because even sophisticated animal models cannot capture features of addiction that are uniquely human, as we discuss next.

Addiction may be uniquely human

The 0/3 crit test may be a face valid model of some of the diagnostic criteria for substance use disorders. However, at least three diagnostic criteria (4) are impossible to model in laboratory animals given their reliance on subjective states that can only be assessed with self-report. These are: (i) subjective craving, (ii) taking the substance in larger amounts or for longer than intended, and (iii) wanting to cease or reduce substance use but being unable to. Although diagnostic manuals do not privilege any particular criteria as essential for diagnosis, the latter criteria may be the core features of addiction. For example, Heather (46) argues that "a person is addicted to a specified behaviour if they have demonstrated repeated and continuing failures to refrain from or radically reduce the behaviour *despite prior resolutions* to do so" (p25 emphasis ours;

see (47-49) for similar arguments). If this view is correct, this raises the question of whether it is possible to capture the core features of addiction in animal models. Punishment schedules (part of the 0 /3 crit model) are able to make negative consequences contingent upon drug self-administration, but they rest on the assumption that if an animal persists with drug self-administration under a punishment schedule, it is doing so despite making a prior resolution to do otherwise. We do not anticipate the future development of an animal model of 'behaving in one way despite intending to act differently', because such a model would require understanding of the animal's subjective state (47).

A broader question is whether addiction can be attributed to 'the animal within us' or the 'human within us' (48). Until fairly recently, the latter view was widely accepted: whilst nonhuman animals could be trained to self-administer drugs, they could never become 'addicted' because of the impossibility of establishing if they were self-administering drugs whilst intending to do otherwise (50). More recently, addiction has been attributed to 'the animal within us': neurobiological adaptations in subcortical regions that are shared between humans and nonhuman animals, such that those regions come to dominate cortical structures that are more developed in humans and other primates (51). However, this conceptualization raises another problem with animal models: if addiction arises, at least in part, because 'human' brain structures are somehow compromised, how is it possible to model addiction in animals that have qualitatively different neurobiology? (48, 52).

A further important difference between animals and humans is their use of language, which plays a key role in the initiation of drug use and recovery from addiction. People initiate drug use if they expect the benefits to outweigh the negative consequences (53-55). These expectations are formed from peers or parents (56) or

advertising (57), before any direct experience of drug use. Compare this with animal models of addiction, where initiation of drug self-administration is either accidental (from the animal's point of view) or forced by the experimenter (40). Language also plays a vital role in treatment and recovery from addiction in humans. For example, the translational failure of memory reconsolidation interventions for cocaine addiction that were discussed earlier (25) could be attributed to a number of factors related to different aspects of memory stabilisation and reconsolidation. However, one explanation for this translational failure is that humans understand experimental procedures in ways that animals cannot (58). Specifically, studies with human participants reveal that memory reconsolidation mechanisms are activated only when the outcome of an event is uncertain (59). Therefore, memory reconsolidation interventions can only work if participants reasonably expect to have an opportunity to receive the drug. Unlike laboratory animals, participants in trials of memory reconsolidation treatments for addictions (e.g., 25) have no reason to believe they may receive the drug during the trial; therefore there is no opportunity for memory reconsolidation to take place. This between-species difference fundamentally changes the context in which memory reconsolidation interventions take place, which may have contributed to the failure to translate findings from animal models to trials with humans.

Additionally, 'talking therapies' such as cognitive behaviour therapy and motivational interviewing, and self-help groups such as Alcoholics' Anonymous are among the most efficacious treatments for addiction (13, 17, 60). These rely on verbal interactions between people with addiction and therapists or sponsors to change psychological constructs such as motivation to change and coping skills. Change in these psychological constructs, which are inferred from self-report, plays a vital role in

recovery from addiction. For example, the effects of cognitive-behaviour therapy on alcohol abstinence among drinkers with severe alcohol dependence are mediated by improvements in coping skills (61). Among patients who receive motivational interviewing in tandem with other behavioural interventions, the extent to which drinkers with alcohol dependence verbalize commitment to change their drinking at the start of treatment predicts treatment success (62). Changing such psychological constructs is not only a key component of formal therapies, but also underpins the effectiveness of self-help groups such as Alcoholics Anonymous that support members to maintain their recovery motivation and boost their confidence that they are able to stay abstinent (60). Therefore, the way people communicate about their drug use influences the trajectory of addiction from initiation to recovery. Animal models cannot model the role of language in addiction, and they will inevitably overlook how language could impact the translation of candidate treatments from animal models of addiction to clinical trials with humans.

Network models expose the limited value of animal models of psychiatric disorders

Network models of psychiatric disorders attempt to model the interplay between different symptoms of disorders (particularly subjective states), and they consider how symptom networks are dependent on the broader environmental context (63). Such models "preclude the identification of a common cause of symptomatology with a neurobiological condition" (Borsboom et al. (63), p1). Network models are highly relevant for addiction (64, 65). For example, the diagnostic criteria (4) of (i) subjective craving and (ii) continued substance use despite intentions to stop are unlikely to each

have their own distinct neural substrates; instead, the former should contribute to the latter. An example that illustrates the crucial role of the broader context is the current opioid crisis in the USA, which can be attributed to deindustrialization, economic decline and urban decay alongside massive increases in the availability of prescription opioids (64). These examples illustrate the futility of attempting to map addiction to brain function independently of the relations between subjective symptoms and the broader environmental context. By extension, this may account for the poor predictive validity and explanatory power of animal models of psychiatric disorders, including addiction (66).

In response, Müller (65) called for "constructive reductionism": a reductionist empirical approach, that would incorporate animal models for testing of specific components of networks including the biological substrates of specific behaviours; combined with a constructivist synthesis of the broader network, that would largely rely on observational rather than experimental methods (e.g. (67)). We agree that sophisticated animal models that incorporate social factors, problem solving and a choice of reinforcers should increase the relevance of animal models of addiction to the human condition (18, 40, 45). However, given its complex nature, we consider it unlikely that animal models will ever be able to model the relations between subjective symptoms and the economic and social factors that determine the onset and persistence of addiction (and recovery from it) in humans.

Conclusions

Animal models of addiction have a poor track record for the identification and development of addiction treatments that have clinical benefit in humans, and their contribution has consistently been misrepresented and oversold. More fundamentally,

animal models have misled us about the very nature of addiction in humans. One might counter that recent refinements in animal models suggest reasons to be optimistic about the future, in particular that we may soon discover the molecular switches that drive persistent drug preference in choice settings (41-43). However, if addiction is indeed 'uniquely human', and largely dependent on language, causal inter-relationships between subjective symptoms, and the broader social, economic and environmental context, then such a rose-tinted view would be unwarranted.

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