The relevance of animal models of addiction

Questioning the utility of animal models is not specific to addiction, but concerns most animal models of higher brain functions and dysfunctions. Such debate is needed, and stimulates progress towards translation.

It is often argued that animal models [1,2] of addiction are limited because they cannot integrate the ‘whole picture’. However, the ‘whole picture’ is probably as difficult to capture in humans and likely to be very different between addicted people [3]. While paths and trajectories may differ, the expression of addiction itself appears more homogeneous and its exploration through animal models is worthwhile.

Clinicians and basic researchers share the view that certain life conditions favor expression of predispositions to psychopathology, including addictive behaviors [4,5]. This context-dependent expression of vulnerability is compatible with both the network models of psychiatric disorders [6] and the opioid crisis, contradictory to what is stated by Field & Kersbergen [7]. It is also not incompatible with mapping expression of addiction to brain function [8,9], together with exploring the role of psychological risk factors [10] contributing to its development. Type 2 diabetes provides an interesting parallel. It is exploding with western life-styles, yet ‘mapping’ diabetes to insulin resistance and studying its biological mechanisms is not questioned. At the same time, it is agreed that the individual risk is not only molecular and biological, but behavioral, and that understanding psychological factors that favor overeating and disadvantage physical activity is as important.

Whether addiction should be classified as a disease is a matter of perspective [11], but no one can deny that drugs users ask for support when their drug-taking becomes maladaptive. Eventually, the threshold between non-problematic and problematic use may vary depending on societies and species, but it might be the pathognomonic symptom of addiction, and key to animal modeling and its translation to humans. In this perspective, initiated for cocaine addiction in the early 2000s, animal paradigms started to test how drug-taking-seeking becomes maladaptive, i.e. resists contingent or concurrent adaptive behaviors. The most emblematic tests are the maintenance of drug-taking-seeking despite the contingent presence of an aversive stimulus (electric foot-shock) or the presence of an alternative natural reinforcer (e.g. sucrose) [12]. Models using choice with alternative reinforcers are therefore not a recent development [7]. An evolution came with the combination of the two types of models (the concomitant choice between punished cocaine use and sucrose) [13,14], and what is highly novel is the use of a social interaction as an alternative reinforcer. In addition, it competes totally with drug self-administration [15] while sucrose reinforcement does not. Such findings should be taken cautiously at this stage: they have been shown only for methamphetamine, and competition with alternative reinforcers may be protocol-dependent [16].

Also, the idea [7] that prevailing animal models portray addiction as a disorder of habit and compulsion is only partially true. Habit has been quickly discarded as a player in cocaine addiction-like behavior as measured in the multi-symptomatic model (called here 0/3 criteria) [17,18], and as confirmed by the puzzle-solving procedure. Regarding compulsion, cocaine-seeking and -taking should probably be dissociated, as recent data (to be further explored) indicate that compulsivity could involve more taking than seeking [16].

In these new models, there are key factors to be considered [2], which can lead to discrepancies or misinterpretations: (1) the protocol used to ‘induce’ addiction-like behavior; (2) the conditions under which addiction-like behaviors are evaluated. Why do more ‘addicted’ rats choose cocaine when faced with negative consequences (approximately 30%) than when offered an alternative sucrose reinforcer (9–15%). Because they have no choice other than cocaine? This is unlikely, as approximately 30% of rats maintain seeking despite punishment, even with concurrent sucrose availability [14]. It eventually appears that the percentage of rats choosing cocaine over sucrose increases when contingency between cocaine and sucrose choice increases [16]. (3) Most critically, a third factor is the threshold to define an addiction-like behavior: where do we place the threshold to define maladaptive drug-seeking-taking? How do we know that it reflects a maladaptive behavior rather than just the expression of a normal continuum of individual differences? Pelloux et al. [13,14] supported [19] that a threshold based on the expression of a bimodal distribution of the population is the most reliable option.

Implementation of these new experimental approaches is still limited, and they are at times reductive, which can diminish their relevance: using the semantics (‘addicted-like’, ‘compulsive-like’) is not enough when describing the 30–35% highest percentile of a normal distribution screened through a test that does not even necessarily evaluate the maladaptive nature of drug use. The bathwater is cloudy, but throwing the baby out with it, i.e. rejecting animal models as a whole, is detrimental.
Declaration of interests

None.

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