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An imperfect model is still useful.

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Concise statement: Although there have been few recent breakthroughs in pharmacotherapies for substance use disorders, animal models continue to offer useful insights into the structural and genetic mechanisms that underlie susceptibility to substance use disorder. They cannot capture all aspects of the human condition; however, they are able to recapitulate certain key endophenotypes, and help us to understand why these occur.

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Field and Kersbergen¹ raise important issues regarding the utility of animal models for understanding and developing new treatments for substance use disorder (SUD). Their argument revolves around four basic tenets: many “treatments” developed in animal models have failed, hence represent a waste of resources; animal models commonly represent drug seeking as an inflexible and habitual behaviour, which is misleading; crucial aspects of SUD, such as language, can never be represented in an animal model; and addiction can only be understood in the context of complex society. An animal model of any complex human condition can, almost by definition, only ever capture certain aspects of said condition. However, we argue there is still value to be gained from such an approach.

Although SUD is notoriously difficult to treat², preclinical animal research *has* uncovered agents that have been translated into effective treatments – as acknowledged. A major difficulty is that SUD is a multifaceted condition. We do not fully understand why or how it develops, why there are individual differences in susceptibility and resistance, and why the behavioural patterns that characterise substance use, once established are so pervasive. While limited, animal models afford control, as well as spatial and temporal resolution to examine these *elements* of addiction-related behaviours. From such building blocks, and with reference to human behaviour, we can develop a greater understanding of addiction.

For example, animal research has given greater insight regarding the neural circuitry that drives drug and alcohol seeking, as well as the complex way different circuits interact to determine when drug-seeking is retrieved or inhibited^{3,4}. Many studies assess this in animals with limited exposure to drugs, that are therefore not ‘addicted’. However, this still provides information about neural mechanisms that initiate drug-seeking. Understanding normal behaviour is the first step toward understanding maladaptive behaviour. Notably, imaging studies show substantial homology between this circuitry in rodents, other non-human animals and that in humans⁵. This implies that findings in animal models, where neural mechanisms can be described with greater detail, can be used to derive hypotheses regarding human neural activity. Researchers are also now studying similar behaviours and brain loci using animals with a more prolonged history of voluntary drug intake⁶, or in animals that show preference for drugs over ‘natural’ reinforcers^{7,8}. This may open the door to understanding differences between normal and pathological reward seeking, as well as brain mechanisms that underly the transition between these states.

Animal research is useful for modelling behavioural features of SUD, such as volition, resistance to punishment, and relapse propensity. For example a recent rat study showed that individual differences in relapse propensity after voluntary abstinence driven by adverse outcomes was mediated by the insula cortex⁹. This finding recapitulates human imaging data showing increased activation of the anterior insular associated with compulsive alcohol seeking¹⁰. Another recent study uncovered a genetic mechanism governing preference for alcohol over a sweet solution. This phenotype, present only in 12% of rats tested⁷, was associated with other behaviours characteristic of alcohol use disorder such as continued use despite adverse outcomes. Most importantly, it was associated with a change in gene expression that was paralleled in post-mortem tissue of humans with alcohol use disorder⁷.

Therefore, animal studies can reproduce key endophenotypes that at least relate to human alcohol use disorders and explore why these occur in some subjects but not others. Increasingly, animal research is embracing individual variability rather than unitary response patterns, and complementary findings between animal studies and human experience have ensued^{7,9,10}. Judicious examination of both intra-species individual differences as well as inter-species similarities may provide a powerful tool for understanding the (patho)physiology that drives maladaptive reward seeking; knowledge that may ultimately lead to more effective strategies for tackling SUD.

A model is only ever that – it cannot capture all aspects of any disorder. Certainly, it cannot capture how language could impact the translation of candidate treatments to clinical trials. However, SUD includes behavioural features that can be modelled in animals, and such models can be used to understand circuitry and genetic mechanisms at a level of precision not always possible with human research. Considered application of findings from animal models can inform human research. Furthermore, findings from human participants can be back-translated and tested in animal models to provide evidence of functional mechanisms driving substance use^{7 11}. We agree that animal models should never seek to replace well-thought out research that examines human behaviour. Animal models do however provide a starting point from where studies in more complex but less controlled circumstances can evolve¹².

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