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EDITORIAL

# Innovating translational models of affective disorders

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The need to better understand and treat affective disorders is a major challenge in psychopharmacology. Despite recognition of the huge societal and personal impacts of affective disorders, advances in our knowledge of the disease aetiologies are surprisingly limited. There is also controversy within the field with strong, and sometimes opposing opinions, amongst different scientists, clinicians, advocates, and patients around some of the very fundamental questions about affective disorders and their treatment. These include debates about the different causal mechanisms that contribute to the development of affective symptoms and the clinical benefits that might be achieved with antidepressant drugs. After several decades of withdrawal of industry investment in psychopharmacology and limited success in developing new treatments, the last decade has seen a renewed interest in the development of new treatments for affective disorders, particularly major depressive disorder (MDD). A major factor in this was the publication by Berman et al. 2000 showing rapid and sustained antidepressant effects with the NMDA antagonist, ketamine that has fuelled a resurgence of interest in the potential for a new class of rapid-acting antidepressants (RAADs). This has been further enhanced by the widespread interest in psychedelic drugs in psychiatry, particularly for treatment-resistant depression, with recent clinical trials finding evidence of efficacy for the serotonergic psychedelic, psilocybin (Goodwin et al. 2022; von Rotz et al. 2023). As well as supporting new interest from industry, the ability of these RAADs to induce these apparently profound and sustained changes in patient's emotional symptoms, offers a potential route to better understand the fundamental biology of emotional regulation and how and why it may become altered in affective disorders. However, just as was the case with the original discovery of antidepressant drugs, these findings are similarly based on clinical studies and the underlying mechanisms that link the drugs biological effects with changes in mood remain unknown. Thus, whilst it is exciting to see new investment in the field many challenges remain particularly in relation to how we use animal models and translate findings from non-human animals to patients with affective disorders.

The first 'animal model of depression' is widely considered to be the forced swim test (FST) and was described in 1977 by Porsolt. Although referred to as a model of depression, the FST is a behavioural method designed to predict antidepressant efficacy. The validation of the model came from studies using known antidepressant drugs which the test could reliably differentiate from other psychoactive substances based on their effects on immobility time in an acutely stressful situation. The FST and related methods have been found to be good predictors of antidepressants acting through monoaminergic mechanisms and possibly glutamate although see (Viktorov et al. 2022), however, there has been a shift in its use within psychopharmacology from a test to predict efficacy to a phenotypic test and to study underlying mechanisms which may be less appropriate (Commons et al. 2017). When considering animal models for studying affective disorders it is important to recognize that there are two distinct elements needed. Firstly, there is a need for a disease model that recapitulates some or all the features of the human condition including involving relevant underlying biology, i.e. construct and face validity. There is also the need for clinically meaningful readout which, in the case of psychiatric disorders, is most likely behavioural as other biomarkers have yet to be identified and validated. When considering the disease model, the risk factors for affective disorders are quite well established and can be used to generate an animal model with a putative negative affective state or depression-like state, such as early life adversity, chronic stress, and interferon-alpha immune challenge. With the ability to link back to epidemiological data, establishing the translational relevance of these models is relatively straightforward. The challenge however is how do you quantify the arising phenotype

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and identify underlying mechanisms and novel drug targets. In patients, most clinical studies define affective symptoms based on clinical interviews and subjective self-report questionnaires. It is impossible to directly translate between these measures and a behavioural readout in non-human animals and so inferences about the relationship between animal behaviour and subjective self-reported symptoms have been made, for example, the FST has been linked to the subjective experience of hopelessness, deficits in sucrose preference in the sucrose preference test are related to the subjective experience of a loss of interest in rewarding activities. Although these may achieve some degree of face validity, they also involve an anthropomorphic interpretation, and it is difficult to know whether they involve similar underlying mechanisms. Whilst sensitive to chronic stress manipulations, many of the studies looking at other risk factors fail to find changes in these readouts (Robinson 2018). Many currently think these conventional 'models of affective disorders' provide a behavioural readout sensitive to acute and chronic stress manipulations but may not be directly relevant to human affective disorders. Similar issues also exist when considering anxiety-related behaviours. The majority of these studies rely on natural behavioural responses of rodents to aversive or fearful situations (e.g., open field arena, elevated plus-maze, novelty suppressed feeding). As with the depression models, these behavioural tests were initially characterised on the basis of the efficacy of known anxiolytics acting via the benzodiazepine receptor, but how well they relate to human pathological anxiety is not clear. The sensitivity of these anxiety tests to serotonergic drugs is also less robust despite these drugs being the most widely used treatments for anxiety disorders. Despite these known limitations many publications involving preclinical studies still use these behavioural readouts. The aim of this special issue was to look at new innovations in the field of animal models of affective disorders and how psychopharmacology is addressing these challenges particularly as the field seeks to not only predict clinical efficacy but also understand relevant underlying mechanisms and identify novel drug targets.

## Contributions to this special issue

The lead theoretical article, by Krishana et al. (2023), illustrates an approach to improve behavioural tasks so they work across species to facilitate translational research with place conditioning, a procedure used with animals to study the rewarding effects of drugs. Often when we think of improving translation, the focus is on developing a task for animals that is more analogous to a task currently in use in humans. This commentary highlights the benefits of taking a task used in animals and adapting it across species including for humans, underscoring the value of back-translation. In addition to improving behavioural tasks, Erdman and Eldar (2023) next advocate for leveraging a computational approach to understanding maladaptive patterns of emotions. They identify three computational factors, self-intensifying affective biases, misestimations of predictability, and misestimations of controllability, that may be responsible for excessive emotions and moods and detail how they can be tested to improve therapeutics.

In the last introductory meta-analysis, Stupart et al. (2022) highlight the limitations of using commonly employed unconditioned procedures, such as the elevated plus maze, open field, sucrose preference test, and FST, for testing affect-related endpoints in rodents. The metanalysis reveals that these tasks do a poor job of revealing differences between rats raised in standard conditions versus rats exposed to maternal separation, which is known for inducing early life stress. The authors argue that using unconditioned procedures in isolation is not thorough enough and instead advocate for employing more objective tasks with the sensitivity to detect alterations in specific cognitive processes to improve translational research. This point is well taken but leaves many in the preclinical research space wondering what tasks we should use instead. Fortunately, the next series of empirical papers begin to address this issue.

One emerging approach is to employ tasks that assess cognitive affective bias (CAB) designed to examine how affective states impact cognition. This approach is detailed in the first original investigation by Aliphon and colleagues (2022) who compare the FST to a rat CAB task, where rats are presented with ambiguous cues from a range of sensory modalities to assess positive and negative bias. Chronic stress causes a shift in the bias from positive to negative. However, there is little relationship between the CAB score and behaviour in the FST, suggesting CAB tasks engage different processes than traditional unconditioned procedures. Another endpoint that is gaining utility in preclinical studies is social vigilance, the exacerbated attention to the social environment that is a symptom of social anxiety disorder. In a particularly clever model that utilizes the California mouse, which exhibits biparental care, Walker and colleagues (2023) detail how paternal deprivation alters offspring sociability, anxiety, and neuroimmune function. A key finding is that paternal deprivation increased social vigilance behaviour in offspring, with some effects more pronounced in females. These changes in vigilance were linked to sex differences in cytokines and stress hormones, providing new potential targets for understanding aspects of social anxiety disorders.

The next series of studies employ effort-based decision-making tasks, where the subject is concurrently presented with a high-effort/high-value reward option or a low-effort/low-value reward option. These tasks have been back-translated to humans and are sensitive to motivation deficits in MDD and schizophrenia, where behaviour shifts towards low-effort/low-value reward choices. Marangoni and colleagues (2023)

adapted the effort-reward task from rats to mice and combined it with video analysis of chow-related behaviours increasing the sensitivity of the measure of low-effort/low-value reward engagement. Matas-Navarro and colleagues (2023) highlight the importance of considering sex and age effects in effort-based decision-making tasks and note important sex differences using palatable reinforcers in mice, where female but not male mice maximize their sucrose intake. Roberts and colleagues (2023) use an effort-based decision-making task in a mouse model of winter gestation, which is a risk factor for several psychiatric disorders. They find that prenatal but not postnatal exposure to a short-active photoperiod reduces preference for the high-effort/high-value reward option versus the low-effort/low-value reward option and implicate dopamine signalling in this effect. Collectively, these studies demonstrate the utility of effort-based decision-making tasks for studying aspects of affective disorders in rodents.

The next series of metanalysis and empirical studies refine our understanding of the processes affected by antidepressants and antianxiety medications with the goal of guiding their use for more effective treatment. Heesbeen and colleagues (2023) used a meta-analysis to reveal that selective serotonin reuptake inhibitors (SSRIs) specifically reduce contextual fear expression and facilitate extinction learning. Groenink and colleagues' (2023) complementary meta-analysis assessed how different anxiolytics alter cued fear versus non-cue-based startle, which is thought to reflect broader anxiety-like behaviour. While several benzodiazepines reduced cued fear, only 5-HT1A antagonists altered non-cued fear. Extending our understanding of the 5-HT1A receptor as a therapeutic target, Papp and colleagues (2023) used 5-HT1A receptor-biased agonists and found that these drugs caused rapid persistent antidepressant-like effects in a rat model of chronic stress, highlighting their therapeutic potential. The final paper by Collins and colleagues (2023) aimed to assess in a preclinical model aspects of SSRI discontinuation syndrome. Using home cage monitoring, they found that sleep bouts were altered for a week following SSRI discontinuation, a phenotype that could be used as a biomarker in future studies aimed at minimizing SSRI discontinuation symptoms. Collectively, this group of studies refines our understanding of how traditional and novel pharmacology treatments and their cessation affect specific aspects of fear, anxiety, and sleep which can guide the optimization of their use to maximize their efficacy in the clinic.

## Summary of current status and future directions

As highlighted in both this special issue and the wider literature, progress has been made in developing more translational models to study affective disorders. These articles also highlight the wider recognition of the need for innovation in this area. Whilst animal models have often been the focus of criticism, there is also a need for objective methods for human research. These measures provide important methods to better understand the human condition as well as a framework for the development of animal models. Rather than a focus on trying to relate animal behaviour to human self-report measures, the shift towards translational methods with relevance across species is an important development. The advances in experimental medicine and the use of objective methods to quantify affective symptoms in patients have enabled preclinical researchers to build from the underlying neuropsychology to create tasks for non-human animals that quantify similar processes. We also see examples of the development of human tasks based on the principles of an animal test. In the absence of any reliable physiological biomarker of affective state, working across species is more challenging. However, as we have seen in this series of articles, if we consider there may be 'cognitive biomarkers' which arise in affective disorders and which can be quantified objectively, then trans-species behavioural tasks and a more translational approach to studying affective disorders becomes possible.

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