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SPECIAL ISSUE/PRECLINICAL ASSAYS

Preclinical animal models and assays of neuropsychiatric disorders: Old problems and New Vistas - introduction to the special issue

Stan Floresco[1] · Angela Roberts[2] · Emma Robinson[3] · Diego A. Pizzagalli[4]

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Abstract
Preclinical research is an essential aspect of biomedical science that aids in clarifying the pathophysiology of underlying illness and devising new treatments. This special issues brings together original research and review papers that pertain to the development of novel models and behavioral assays of symptoms of neuropsychiatric disorders, which may help to refine preclinical studies and to improve their translatability to the human condition.

Keywords Animal models · Depression · Emotion · Motivation

Preclinical research represents an essential step for providing a better understanding of the pathophysiology underlying different illnesses and harnessing this information to develop novel treatments. Among the biomedical fields, research examining neural abnormalities that characterize neuropsychiatric disorders has been particularly challenging, as these research endeavors often suffer poor animal-to-human translation. This has been referred to as "death valleys" of the translational continuum (Grottick et al., 2021), wherein purported treatments translated from animal models relevant to mental illnesses often fail to effectively treat target symptoms when tested in clinical trials with patients. These translational gaps may stem in part from issues relating to the specific experimental manipulations used to model neural perturbations associated with a disorder. Perhaps more critically, the cognitive/emotional processes measured with behavioral tests used with animal models may not always be related to those processes altered in humans with mental illness. A critical evaluation of these issues and the development of novel models and behavioral assays of symptoms of neuropsychiatric disorders may help to refine preclinical studies and improve their translatability to the human condition. This Special Issue brings together scholars discussing contemporary issues surrounding preclinical studies relevant to neuropsychiatric disorders and novel approaches to tackling these issues. A particular emphasis is placed on identifying transdiagnostic approaches to model and assess specific dimensions of behaviors, in keeping with the Research Domain Criterion framework (Morris et al., 2022).

This Special Issue includes studies using both rodents and primates as model systems and probing a broad constellation of functional domains, including *reinforcement/reward learning* (Luc & Kangas, 2024; Neville et al., 2024), *reward prediction errors* (Kehrer et al., 2024), *effort-based decision making* (Noback et al., 2024), *decision-making with delayed punishments* (Minnes et al., 2024), *judgement bias* (Neville et al., 2024), various *cognitive functions* (attention, spatial working memory, behavioral flexibility, motivation, recognition; Murai et al., 2024), as well as *attention and impulsive behavior* (Benn & Robinson, 2024). Such domain-specific articles are complemented by empirical and reviews articles focused on preclinical models directly relevant to depression, anxiety, and fear (Drzewiecki & Fox, 2024; Gencturk & Unal, 2024) as well as obsessive compulsive disorder (Pickenhan & Milton, 2024).

Historically, "traditional" preclinical models relevant to depression and anxiety were validated based on their ability to predict the efficacy of drug treatments, but this has limitations for evaluating novel drug targets and interpreting mechanistic studies. Although some aspects of these behavioral tests could be related to subjective symptoms in humans—for example, the forced swim test as a measure of

✉ Stan Floresco
floresco@psych.ubc.ca

[1] University of British Columbia, Vancouver, Canada

[2] University of Cambridge, Cambridge, UK

[3] University of Bristol, Bristol, UK

[4] Harvard Medical School, Boston, MA, USA

"hopelessness" or behavioral despair—whether these behaviors engage relevant neurobiology and hence construct validity is difficult to establish. Accordingly, the current Special Issue starts with three comprehensive reviews that provide in-depth discussion of preclinical assays relevant to depression, anxiety disorders, and obsessive compulsive disorders.

In the first review, Gencturk and Unal (2024) provide a thoughtful review of preclinical assays used to quantify behaviors relevant to depression and anxiety with a focus on construct validity. The authors provide a comprehensive and critical appraisal of traditional methods and then consider whether tasks designed to capture aspects of cognitive affective biases might address these challenges. They also explore how future methods could integrate behavioral monitoring and morphological analysis to better understand the construct validity of these tests.

In the second review, Drzewiecki and Fox (2024) consider the heterogeneity of anxiety disorders and how phenotypic heterogeneity relates to current understanding of anxiety-related neurocircuitry in animal models and highlight emerging approaches to bridge translational gaps. They highlight reverse translation of specific human symptoms using multiple animal models, including atypical rodent species and nonhuman primates, computational modeling for guidance of theory construction and more effective forward translation of basic neural circuitry from preclinical rodent and primate models to test predictions about human anxiety.

In the third review, Pickenhan and Milton (2024) focus on obsessive compulsive disorder, which is a complex and heterogeneous disorder with animal models traditionally defining the model's phenotype based on an exaggeration of behaviors within the animal's normal repertoire (e.g., excessive grooming). It could be argued that the increased expression of certain behaviors relative to control populations aligns with some aspects of the human condition but, as is a common theme for this Special Issue, it is difficult to know whether these are mediated by similar underlying mechanisms. Pickenhan and Milton (2024) discuss these issues and then focus on the Observing Response Task, a translational task designed to capture in nonhuman animals the maladaptive checking observed in patients. Critically, the Observational Response Task quantifies both functional and dysfunctional checking behaviors in an operant appetitive task. This offers many advantages over traditional approaches and the potential to identify relevant neurobiology and novel approaches to treatment.

These initial reviews are followed by a trio of empirical papers probing different facets of the RDoC's Positive Valence Systems. *Motivational deficits* and *reduced reactivity to pleasurable stimuli* are debilitating symptoms that cut across neuropsychiatric disorders, including depression and schizophrenia. One way to assess these functions is by examining how much effort a subject may be willing to exert to procure rewards, which can be measured with progressive ratio breakpoint task that has been developed for use with humans based on procedures initially used with rodents. Using these procedures, Noback & colleagues (Noback et al., 2024) investigated how amphetamine may enhance motivation in humans and mice and how these treatments affect EEG biomarkers associated with task performance. As expected, amphetamine increased motivation in humans, an effect replicated with certain doses of this drug in mice. Task performance also was associated with changes in EEG profiles across both species, yet these profiles were unchanged by amphetamine. This latter finding suggests additional studies are needed to identify biomarkers that may predict how certain drugs may enhance motivational processes.

Luc and Kangas (2024) describe validation studies in mice using a Probabilistic Reward task, which was initially designed to identify reinforcement learning deficits in human clinical populations (Pizzagalli et al., 2005). These processes tap into the heterogenous and somewhat poorly defined concept of "anhedonia," prevalent across numerous mental illnesses, which in humans has traditionally been measured with self-reports. In comparison, animal studies often use rudimentary sucrose preference assays, which show poor translation to humans with depression (Dichter et al., 2010; Wang et al., 2022). In this study, the authors describe novel procedures for using this Probabilistic Reward Task in mice, which are commonly used in preclinical neuropsychiatric research. Moreover, they also observed robust cross-species continuity when comparing they key performance metrics across mice, rats, and primates, suggesting this assay may have great utility in identifying mechanisms and potential treatments for anhedonic disorders.

The Reward Positivity (RewP)—an event-related potential that can be recorded over frontocentral scalp electrodes when humans receive a reward—has emerged as a potential transdiagnostic biomarker of reward responsiveness, learning, and valuation relevant to a range of disorders, including depression, schizophrenia, Parkinson's, and substance use disorders. Recently, a rodent homolog of this reward-specific signal has been reported in the delta band of field potential responses. Kehrer & colleagues (Kehrer et al., 2024) further elucidate the cortical source of the signal, revealing it to be strongest in ventral regions of the rodent medial prefrontal cortex. The comparable timeframe of these responses to phasic midbrain dopamine neuron responses to reward in humans and mice is suggestive of cortical-subcortical integration and further reinforces the validity of this translational biomarker.

Another domain disrupted in conditions, such as depression and substance use disorder, is *maladaptive sensitivity to negative consequences of one's decisions*, and this can be more prominent when these outcomes occur after actions are taken. However, there have been few preclinical studies

probing the neurochemical underpinnings of how delayed punishment might influence actions selection. Minnes & colleagues (Minnes et al., 2024) discuss their procedures wherein rats choose between smaller versus larger rewards, the latter of which also coincided with footshock punishment that occurred with varying delays after a choice. Intriguingly, delays to punishment markedly attenuated their ability to bias choice away from larger rewards. Moreover, they showed that potentiated catecholamine transmission could, under some conditions, enhance delayed punishment sensitivity, pointing to these systems as potential targets for treating suboptimal decision-making in neuropsychiatric disorders.

These empirical papers focusing on reward or punishment processing are complemented by two articles focusing on cognitive function and attention. First, *impairments in cognitive function* are pervasive across psychiatric and neurological disorders, particularly in aging populations and those afflicted with Alzheimer's disease. Although there are numerous assays to probe these functions in rodents, preclinical studies with these animals often fail at identifying cognitive-enhancing treatments that have clinical benefits in humans. As such, assessing these functions in primates may provide better translational value, as this species display a more prolonged prodromal phase in cognitive decline that more closely resembles that seen in humans. To this end, Murai & colleagues (Murai et al., 2024) detail their work establishing comprehensive battery of touchscreen-based tasks that capture a spectrum of domains sensitive to detecting aging-related cognitive decline in marmosets. Their work shows how this battery can assess multiple domains of cognition within-subjects and is suitable for repeated testing that can measure progressive changes in function across different points in lifespan.

Second, *attentional deficits* are prevalent across numerous psychiatric and neurological conditions. Enhancing catecholamine transmission with either stimulant and nonstimulant drugs has been found to improve attention in humans and animals tested on a variety of tasks, although it has been difficult to disentangle if they do so through similar or differing mechanisms. Benn and Robinson (2024) describe their work translating a human rapid serial visual presentation task for use with rats and compared the effects of different medications known to improve attention. Using these procedures, they reveal that drugs like amphetamine, atomoxetine, and methylphenidate differentially affect attention and impulsivity.

The current Special Issue ends with a thoughtful primer by Neville & colleagues (Neville et al., 2024), which emphasizes both the challenges and opportunities of preclinical investigations probing cognitive, motivational, and affective processes. In light of the complex relationships between domains of functioning and underlying neurobiological and cognitive mechanisms, the authors cogently argue that computational modeling provides a unique platform to 1) compare and integrate findings across species, and 2) disentangle processes underlying specific behavioral choices. Taking a "computational psychiatry" approach is associated with several important features. First, computational models can be used to generate new (emerging) hypotheses, which can then be empirically tested. Second, demonstrating that a given manipulation (e.g., a pharmacological challenge or stressor) affects the same computational parameters across species (e.g., rats, humans) provides some of the most compelling evidence of confluence across species (for a discussion, see Pizzagalli, 2022). Third, and critically important, by developing models or classifiers of facial expressions in animals as proxy of their postulated affective states (Dolensek et al., 2020), the field of computational psychiatry can contribute to the welfare of experimental animals.

Collectively, the ten empirical and review articles included in this Special Issue, along with brief commentaries by ten leading researchers, paint a remarkable array of progress in developing and optimizing preclinical assays that probe functional domains across species with increased sophistication and precision. Often harnessing modern technologies that allow the deployment of complex tasks that are functionally analogous to those used in humans, these studies point to substantial promise toward a better understanding of the neurobiological underpinning of neuropsychiatric disorders. Critically, such preclinical assays promise a faster, and hopefully more reliable, translation between experimental animals and humans, and thereby accelerate the development of much-needed, novel treatments. Equally important, this collection of articles and commentary also discuss the challenges and opportunities that lie ahead. Ultimately, it will be by overcoming such challenges and embracing such opportunities that the field will deliver a better understanding and treatment of neuropsychiatric disorders that are associated with much personal suffering and societal burden.

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