Perspectives on Behavior Science (2025) 49:9–26
https://doi.org/10.1007/s40614-025-00478-w

THEORY & PHILOSOPHY CONFERENCE PROCEEDINGS

Reverse Translation

Brian D. Kangas[1]

Received: 15 May 2025 / Accepted: 28 August 2025 / Published online: 19 September 2025
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Abstract

Stagnation in the development of novel strategies for the management of major depression and other neuropsychiatric disorders has left many patients with unmet treatment needs. This state of affairs has encouraged critical appraisal of the very relationship between preclinical findings and their clinical applications in psychiatric practice. One consequence of such reflection has been a growing emphasis on *reverse translation* in preclinical research. Traditional preclinical approaches with laboratory animals have most often used a forward translational approach designed to identify classes of organized animal behavior that serve to predict outcomes in humans. On the other hand, reverse translational approaches identify patterns of human behavior revealed by task performance to develop assays with maximal formal similarity in laboratory animals. Presumably, such correspondence will evoke functionally similar behavioral outcomes across species, allowing for rigorous assessment of innovative, sometimes invasive, behavioral and pharmacological treatment strategies impossible to examine in human subjects without substantial preclinical evidence of safety and efficacy. Following validation and optimization, a reverse translational framework can be used for coordinated bidirectional pursuits across species to accelerate the drug discovery process. To aid appraisals of emerging reverse translational techniques, the present review outlines five considerations based on their longstanding association with rigorous assessments in behavioral science and informed by behaviorist traditions. Emphases on behavior, pharmacology, environmental determinants, levels of analysis, and cross-species continuity are discussed, with an emphasis on the Research Domain Criteria (RDoC) framework to advance innovative therapeutic strategies for treatment-resistant neuropsychiatric illness.

Keywords Animal models · Cross-species continuity · Medications development · Anhedonia · Major depression · Neuropsychiatric disorders

✉ Brian D. Kangas
bkangas@mclean.harvard.edu

[1] Harvard Medical School, McLean Hospital, Belmont, MA, USA

Biomedical research using nonhuman animals has contributed information critical to the development of behavioral and pharmacological strategies for the management of neuropsychiatric disorders. These efforts also have provided important clues regarding neurobiological mechanisms that may mediate affective disorders, substance use disorders, and other neurobiological maladies. The steady advance in our understanding and in the quality of therapeutic interventions can be directly traced to our ability to conduct rigorous studies in laboratory animals with key variables manipulated with precision under carefully controlled environmental conditions. An underappreciated facet of such research is that, per ethical guidance by scientists, veterinarians, and lay members of the community, studies can be designed to responsibly investigate novel therapeutic avenues that, without costly and time-consuming confirmation of safety and efficacy, cannot be studied in human subjects.

Notwithstanding the many therapeutic advances provided by carefully controlled studies in laboratory animals, it is also important to note research domains that are stagnant (i.e., areas of investigation in which animal models have not yet been associated with such success) and, if possible, what factor(s) may be responsible. This exercise may help determine whether the slow pace of progress is attributable to unique technical challenges in that research domain or, alternatively, to flaws in the methodological approach. In some instances, the area might benefit from a paradigm shift in the ways in which organized animal behavior is arranged and translationally leveraged to provide predictive indices of human outcomes. The present article discusses a prominent example of stagnation, and how recent variations in translation science known as *reverse translation* are developing in ways that address the problems and advance the field.

On the Development of Therapeutic Strategies for Neuropsychiatric Illness

One prominent and timely example can be found in the stagnation that characterizes the development of novel treatment strategies for major depressive disorder. Despite a well-publicized *mental health crisis* that has grown in recent years (Substance Abuse & Mental Health Services Administration, 2022), conventional frontline antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), leave many patients with unmet treatment needs. Indeed, only approximately one third of those diagnosed with major depression are estimated to report full clinical and functional recovery following standard SSRI treatment regimens (Al-Harbi, 2012; Sussman et al., 2019). Although recent and highly publicized pharmacotherapeutic advances, such as the U.S. Food and Drug Administration (FDA) approval of esketamine (Kim et al., 2019) and ongoing Phase III clinical trials of psilocybin (Goodwin et al., 2022), are promising, there is a widely recognized need for additional non-SSRI alternatives among treatment-resistant populations. Yet, progress on this front has been stubborn and slow.

There are several reasons for this stagnation, including our incomplete understanding of the etiology and pathophysiology of depression. However, the qualitative differences in preclinical and clinical assays of depressive phenotypes may

be the most problematic feature of current research in this domain. For example, the most common animal model of depression-related behavior is the forced swim test in which rodents are immersed in water and the proportion of time engaging in escape-related behavior and immobility is examined (Porsolt et al., 1977). Although this approach, which features relatively high throughput of rapid drug screening at low costs, has for many years yielded data that have assisted the development of medications for depression, interpretive caution is required (Molendijk & de Kloet, 2022). It is difficult, at best, to conduct parallel studies in human subjects to evaluate the translational value of this methodology. Moreover, although the forced swim test has been used effectively to identify SSRIs (Petit-Demouliere et al., 2005), medications development for treatment-resistant depression, by definition, demands the identification of non-SSRI approaches.

Put another way, a paradigm shift in novel preclinical approaches in which the functional target and, hence, applicable methodology, is reconceptualized may be a necessary step in the identification of next-generation atypical antidepressants. Indeed, the need for (and evidence of) such a paradigm shift has already been offered by the major funder of depression treatment research in the United States, the National Institute of Mental Health (NIMH). Thus, the NIMH in recent years has heavily discouraged the use of traditional animal models of depression, including the forced swim test (Reardon, 2024), and instead has expressly emphasized an empirical embrace of behavioral complexity, underlying neural systems, and functional phenotypic domains with more direct translational relevance to psychiatric disorders in humans (NIMH, 2019).

Given this state of affairs, good faith discussions regarding the ability of animal models to contribute translationally relevant indices of complex—and, perhaps, uniquely human—heterogeneous conditions have ensued in recent years (Gyles et al., 2024; Nestler & Hyman, 2010; Robinson, 2025; Silverman et al., 2020; Witkin et al., 2025). Although animal models provide translationally valuable information in a number of research areas, determining behavioral phenotypes relevant to major depression and other affective disorders that can be isolated and objectively studied in laboratory animals is no trivial assignment. Nor is it a new venture. Sixty-five years ago, in the opening chapter of *Tactics of Scientific Research*, Sidman (1960) anticipates this very issue and highlights the challenges inherent in this thorny endeavor of translation from humans to laboratory animals.

> Suppose we are interested in the problem of human depression following the death of a loved one, and we feel that the investigation could profitably be carried out in the animal laboratory. Our task is not simply to find a monkey who will go into a depression when its mate dies. Our course of action will be, rather, to apply to the monkey those behavioral principles that we suspect are operative in the human case. We must create the appropriate conditions in the laboratory so that we may then manipulate them and examine their respective contributions. . . . Will the behavioral changes in the laboratory monkey be similar in principle to the type of human depression in which we are interested? . . . We may not have the whole story, but we shall have made a start toward the identification of critical factors. Carrying out such an experiment

> with a monkey does not, of course, guarantee an increased understanding of the human behavior. . . . An even more serious bar to extrapolation, however, will be the scarcity of objective data on the human side. While the monkey's behavior can be investigated extensively and thoroughly, our control and observational techniques on the human side are likely to lag far behind. Extrapolation from the monkey will be difficult because the case to which extrapolation is to be made will in many instances be poorly defined. Nonetheless, the possibility of obtaining the desired clarity of definition is one of the chief values of experimentation designed to establish a behavioral phenomenon in the laboratory. . . . Like any act of induction, they will be the product of careful experimentation and a creative imagination. (Sidman, 1960, pp. 27–29)

In addition to describing with astute eloquence the complexities of determining translationally relevant behavioral phenotypes in laboratory animals, Sidman was also correct to highlight problems stemming from a "scarcity of objective data on the human side" that, unfortunately, remains the case to date. For example, overreliance on self-report questionnaires for diagnostic guidance currently characterizes clinical studies of novel therapeutic approaches. Although standard diagnostic indices have been promulgated and updated across the five volumes of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), there has been increasing recognition that known heterogeneity within and across various neuropsychiatric diseases is obfuscated by the symptom clustering required for clinical diagnoses. Moreover, in addition to obvious subjectivity and contextual control inherent in self-report questionnaires, they are not easily aligned with modern integrative and systems neuroscience approaches, which span multiple levels of analysis from genomics to neural circuits to organismic behavior.

In response to the overreliance on self-report questionnaires as clinical scales, and its perceived contribution to the widely recognized stagnation in developing new psychiatric treatments, a consensus toward an alternative approach emerged and was outlined by the Research Domain Criteria (RDoC; Cuthbert & Insel, 2013; Insel et al. 2010; Morris et al., 2022). The RDoC provides a unique research framework in which multidisciplinary biobehavioral approaches to study key aspects of neuropsychiatric disorders are used to advance therapeutic strategies. To accomplish this goal, the RDoC empirically defines and optimizes a taxonomy of psychiatric processes, their psychological components, and underlying neurobiological mechanisms that contribute to healthy human behavior. Broad functional domains (e.g., cognitive processes, reward systems) containing more specific dimensional constructs (e.g., working memory, attention) are further defined jointly by behavioral data and neural systems analysis. The resulting biobehavioral road maps allow for easier identification of affected elements during various disorders. This RDoC framework, designed to be data-driven and evolve on the basis of neurobehavioral discovery, represents a major advance, both conceptual and pragmatic, in psychiatric research. Fortunately, the field has never been better positioned to move forward, given ongoing development and increased sophistication of methodologies, ranging from touchscreen-based and other computerized apparatus for the evaluation of complex behavior to functional neuroimaging and electrophysiological recording

techniques, now commonplace in the clinical laboratory with which to analyze underlying neural mechanisms.

Forward versus Reverse Translation

An embrace of behavioral complexity via the RDoC framework also provides an excellent opportunity to advance preclinical research. This can be achieved by characterizing in human patients, relative to their matched healthy control subjects, the critical behavioral phenotypes and key neural biomarkers to be prioritized when identified in laboratory animals. Here, we may draw a distinction in translational endeavors between forward and reverse translation. *Forward translation* refers to the traditional preclinical strategy of identifying and isolating classes of organized animal behavior that might serve as effective predictors of outcomes in humans. On the other hand, *reverse translation* refers to the practice of identifying and isolating patterns of human behavior revealed by task performance to aid development of analogous assays for laboratory animals. Reverse translated tasks prioritize maximal formal similarity of those used with humans to increase the probability that they will evoke functionally comparable behavioral outcomes in animals. The obvious advantage of reverse translation paradigms is the allowance for rigorous assessments of innovative, sometimes invasive, behavioral, neurological, and pharmacological treatment strategies that, in the absence of substantial safety and efficacy data, are impossible to similarly examine in human subjects.

Probabilistic Reward Task: A Case Study in Reverse Translation

Fortunately, there are now multiple examples of the great value of reverse translational approaches and their promise for accelerating the development of novel therapeutic strategies for treatment-resistant depression (Dexter et al., 2025). For the purposes of the present review, the Probabilistic Reward Task (PRT) serves as a particularly instructive example. Initially designed to examine sensitivity to reward in children with attention deficit hyperactivity disorder (Tripp & Alsop, 1999), the PRT was developed further by Pizzagalli et al. (2005) as a means to objectively quantify anhedonia. *Anhedonia* can be operationally defined as the loss of pleasure or lack of reactivity to previously reinforcing stimuli. Anhedonia is of paramount importance because, in major depression, it has been associated with a host of negative outcomes, including poor response to pharmacological medication, cognitive behavior therapy, and neurostimulation, which can result in disease chronicity and increased suicide risk (Admon & Pizzagalli, 2015; Whitton et al., 2015). Moreover, anhedonia is also a cardinal symptom of other neuropsychiatric conditions, including bipolar disorder (Leibenluft et al., 2003), schizophrenia (Moran et al., 2022), posttraumatic stress disorder (Vinograd et al., 2022), and substance use disorders (Koob, 2022). It is critical to note that hedonic tone is not usually restored by conventional SSRI antidepressants and, to date, FDA-approved medications to explicitly treat anhedonia do not exist. This is

especially problematic because positive mood restoration is currently not a *DSM-5* diagnostic criterion for major depression (American Psychiatric Association, 2013) or a criterion for FDA-medication approval, despite the fact that depressive patients most often consider recovery to be a restoration of positive mood rather than a reduction in depressed mood (Zimmerman et al., 2012).

The PRT was designed to supplement traditional self-report questionnaires of anhedonia by embracing behavioral complexity via two rigorous and well-established methodologies to determine a patient's responsiveness to reward. In particular, quantitative models designed to unify behavioral principles of signal detection theory (Gescheider, 2013; Green & Swets, 1966) and the matching law (Baum, 1974; Herrnstein, 1961) within the same framework are used to account for response allocation during conditions of concurrent discriminative choice (Davison & Tustin, 1978). In turn, this framework allows for an objective quantification of adaptive behavior in healthy subjects. On the other hand, deviations from normative observations serve to define aberrant behavioral phenotypes, indicative of deficits in sensitivity to reward as a surrogate for anhedonia (Luc et al., 2021). In this computerized task, human subjects make rapid and difficult visual discriminations (long vs. short line lengths of a mouth on a cartoon face) in which correct responses in the presence of one stimulus (rich) are reinforced three times more often than correct responses in the presence of the other stimulus (lean). Incorrect responses are never reinforced. As documented across numerous PRT studies (Fletcher et al., 2015; Pizzagalli et al., 2005, 2008b, 2020; Vrieze et al., 2013; to name a few), healthy control subjects reliably develop an adaptive response bias towards the more richly reinforced stimulus, whereas subjects with anhedonia often display a blunted response bias that has been shown to reflect their level of anhedonia in established clinical measures, such as the Beck Depression Inventory-II (Beck et al., 1996).

Response bias can be objectively quantified in the PRT using the following equation that is a product of unified signal detection and matching law theories:

$$\log\ b = 0.5 * \log\left(\frac{\left(Rich_{Correct} + 0.5\right) * \left(Lean_{Incorrect} + 0.5\right)}{\left(Rich_{Incorrect} + 0.5\right) * \left(Lean_{Correct} + 0.5\right)}\right)$$

High response bias (log b) values are produced by high numbers of correct responses in the presence of the rich stimulus and incorrect responses in the presence of the lean stimulus, both of which are expected adaptive psychophysical responses under these asymmetric probabilistic contingencies (McCarthy, 1983).

Task discriminability, which quantifies the ability of the subject to effectively engage in the task, is a critical supplementary metric, especially during pharmacotherapeutic treatment and is calculated using the following log d equation:

$$\log\ d = 0.5 * \log\left(\frac{\left(Rich_{Correct} + 0.5\right) * \left(Lean_{Correct} + 0.5\right)}{\left(Rich_{Incorrect} + 0.5\right) * \left(Lean_{Incorrect} + 0.5\right)}\right)$$

High task discriminability (log d) values are produced by high numbers of correct responses for both rich and lean trials, similar to standard percent correct

accuracy measures but on traditional signal detection logarithmic coordinates. A value of 0.5 is added to all parameters in both equations to address instances in which log transforms are impossible, for example, if no errors are made on a given trial type (Hautus & Lee, 1998).

The demonstrated value of the PRT to objectively quantify anhedonic phenotypes as an alternative or supplement to self-report questionnaires, was codified by the RDoC in its most recent revision (NIMH, 2016), in which the PRT was recommended for probing the positive valance system. Notwithstanding theoretical advances in RDoC taxonomy, interpretive caution is required throughout empirical validation of reverse translated systems and underlying methodologies. Although success will ultimately be confirmed by the development of novel and innovative therapies for treatment-resistant patient populations, factors that have been long associated with success in behavioral science may accelerate the search.

Considerations in Reverse Translation

Using the PRT as a case study in reverse translation, the following section describes five considerations that are informed by behaviorist traditions and have displayed longstanding value within the interpretive system of the experimental analysis of behavior (perhaps best typified in Sidman, 1960). These considerations, summarized schematically in Fig. 1, are not intended to be overly rigid or prescriptive but, rather, an outline of elements to contemplate during the development and subsequent optimization of reverse translated approaches.

Behavior

The primary reason to frame task validation and subsequent optimization within the framework of the experimental analysis of behavior is the express priority of rigorous and reproducible behavioral outcomes in such pursuits. The first step of reverse translation involves identifying a human task that has already demonstrated value for characterizing behavioral phenotypes associated with neuropsychiatric illness. These behavioral phenotypes are often defined by their deviation from patterns of performance in healthy control subjects. Next, it is useful to be able to relate particular formal task variables to functional outcomes in human task performance to retain critical features in the laboratory animal assay. In this regard, assigning priority to functional outcomes has served behavioral science well. However, the extent to which formal variables, such as stimulus features and contingency parameters, can be made functionally similar across species has great value for eventual alignment in bidirectional endeavors, in which the human task might need modification.

In the case of the PRT, it was first reverse-translated for laboratory rats by Der-Avakian et al. (2013) following its development and empirical validation of its ability to objectively quantify anhedonic phenotypes in clinical studies of depression (Pizzagalli et al., 2005). It is noteworthy that, whereas the human PRT is a computerized task based on visual discrimination, the original rat version was developed using standard operant conditioning chambers in which subjects were trained

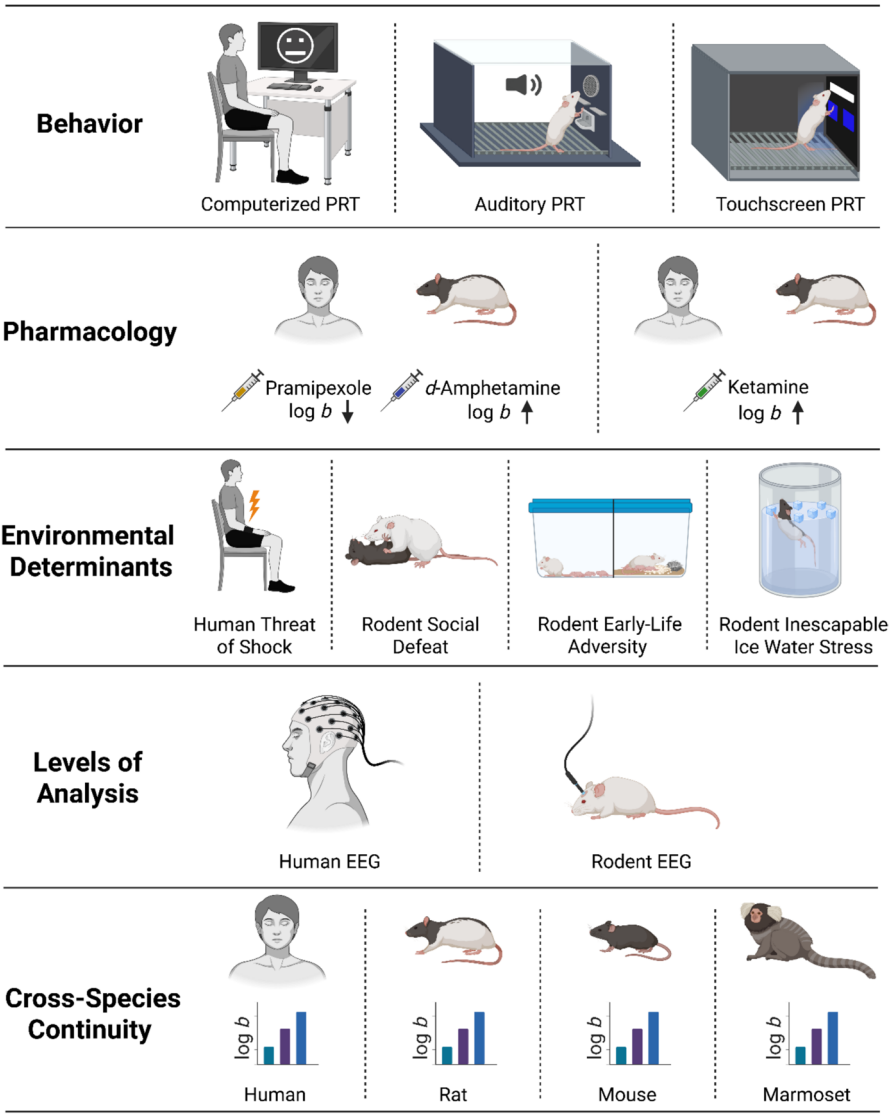

Fig. 1 Schematic Depictions of Five Considerations during the Development, Empirical Validation, and Optimization of Reverse-Translated Paradigms, using the Probabilistic Reward Task (PRT) as an Exemplar

to discriminate between two auditory tones that varied in duration by responding on one of two levers. Notwithstanding differences in task stimuli and dimension (visual line length vs. auditory tone duration), reinforcement contingencies were identical to those in the human PRT, that is, correct responses in the presence of one stimulus were three times more likely to be reinforced (rich) than correct responses in the presence of the other stimulus (lean). Results indicated that response biases for the

rich stimulus in rats (log *b*: 0.2–0.3; log *d*: 0.5–0.6) approximated those previously observed in healthy human subjects (log *b*: 0.2–0.25; log *d*: 0.7–0.9), highlighting excellent control of organized behavior via asymmetric probabilistic reinforcement contingencies quantified within a rigorous signal detection framework. In the further refinement of this promising reverse-translational approach, a subsequent version of the PRT designed for rats incorporated touchscreen technology (Kangas & Bergman, 2017) to permit the use of formally similar stimuli (long vs. short line length discrimination), yielding highly similar outcomes (log *b*: 0.25–0.35; log *d*: 0.8–1.0) as the previous human and rat studies. Together, the behavior selected for study (response bias) was robust across preparations allowing for its manipulation in an advantageous manner.

Pharmacology

In most instances, behavioral task alignment will provide the means for assessing medication strategies across species, indicating the need to verify functional similarity in pharmacological outcomes. For example, bidirectionality in reward responsiveness that had been reported to be mediated by dopamine in human subjects also was evident in the auditory version of the PRT. In both instances, treatment with low doses of the dopamine D_2/D_3 receptor agonist pramipexole blunted, whereas the psychomotor stimulant d-amphetamine enhanced, response bias (Der-Avakian et al., 2013; Lamontagne et al., 2018; Pizzagalli et al., 2008a). In recent research, studies of human subjects and rats using the touchscreen-based PRT have provided further pharmacological validation, documenting close correspondence in the ability of ketamine to enhance response bias (log *b*) for the richly reinforced stimulus without disrupting task discriminability (log *d*) in depressive human subjects and chronically stressed rats (Bogdanov et al., 2025). These latter findings provide a translationally coherent basis for understanding ketamine's utility in the management of treatment-resistant depression and, as well, support the continued value of the PRT as a reverse-translated tool in the drug discovery process.

Environmental Determinants

An additional layer of validation in reverse translational approaches includes the incorporation of relevant environmental determinants in the neuropsychiatric disorder under investigation. In the case of major depression, early-life adversity and chronic stress have been long associated with the development and perseveration of affective deficits (Davis et al., 2017; Hammen et al., 2009; Kessler, 1997; Short & Baram, 2019). Although variables such as early-life adversity and chronic stress can only be documented in clinical cases and not empirically arranged, functional analogs can be designed and investigated in preclinical studies. As with the accommodation of species-specific biological constraints during task development, environmental considerations, such as species-specific features of early-life adversity or, alternatively, acute or chronic stressors with ecological validity, can be prioritized to enhance predictive validity (Juavinett et al., 2018; Lyons et al., 2023). In the case of the PRT, a variety of environmental

manipulations, for example, social defeat stress during adulthood (Der-Avakian et al., 2017), social defeat stress during adolescence (Hisey et al., 2023), chronic mild stress (Lamontagne et al., 2018), the limited bedding and nesting model of early-life adversity (Kangas et al., 2022b), and ecologically relevant thermal stress (Gonzalez et al., 2024) have been used to produce anhedonic behavioral phenotypes in rodents. Despite the diversity of stress modalities, functional and translationally meaningful equivalence in outcomes have been reported. That is, in each case PRT response bias in rodents was significantly blunted, often by a > 50% reduction in log *b*, in a manner consistent with the effects observed in patients with early-life adversity or chronic stress histories (Cunningham et al., 2021; Esfand et al., 2024) and laboratory-based studies of acute stress exposure in humans (Bogdan & Pizzagalli, 2006; Bogdan et al., 2011), encouraging further confidence in translational relevance.

Levels of Analysis

A key advantage of preclinical research in laboratory animals is the availability of mechanistic pursuits in systems neuroscience that involve precise, if invasive, neural recordings. In keeping with the spirit of reverse translational endeavors, however, noninvasive neurophysiological approaches that are used in clinical research should be prioritized. One example is the use of electroencephalogram (EEG) methods to capture real-time neuronal responses during task performance (Carr, 2025). Doing so allows neural analyses, including stimulus-, response-, and reinforcement-locked reactions in the modulation of electrical activity in brain regions or circuits relevant to cognitive behavior such as reward processing (Kangas et al., 2021). Moreover, EEG can be used in reverse translated tasks to identify translational biomarkers offered by neuro-oscillatory responses (Javitt et al., 2020) and event related potentials (ERPs), creating another important bridge between preclinical and clinical research that can provide insight into drug mechanism and further accelerate the development of therapeutics (Blokland et al., 2015).

Within the context of the reverse translated touchscreen-based PRT for rats, Iturra-Mena et al. (2023) implanted local field potential wires and skull screw electrodes in a variety of key brain regions relevant to reinforcement learning. ERP and time frequency spectral analyses identified concordance across species and documented robust neurophysiological signatures of reinforcement learning that are similar to those observed in human EEG studies (Carlson et al., 2011; Santesso et al., 2008; Whitton et al., 2016). These findings highlight neural signatures of reinforcement learning using electrophysiology and touchscreen PRT in rats that are consistent with the possibility that rats and humans share similar neural mechanisms regulating these complex neurobehavioral phenomena. By expanding the reverse translational platform to include other levels of analysis, here electrophysiological biomarkers, such concurrent approaches can provide innovative cross-species means to multimodally appraise candidate therapeutics for anhedonia and other conditions in which reinforcement learning is impaired.

Cross-Species Continuity

Modifications in task structure to best accommodate the biologically determined features of the animal species under study should be considered thoughtfully during reverse translation. For example, the rat is a notoriously nonvisual species. Nevertheless, stimulus control in touchscreen-based line length discrimination is readily obtained in the rat by presenting large salient stimuli, illustrating the importance of functional, rather than simply formal, equivalence of task parameters across species. Further, predictive confidence in a reverse translated task and its utility can be enhanced by demonstrating its functional continuity across multiple species. For example, the similar functional utility of a task in mice, as in rats, not only extends its cross-species continuity but also does so in a species in which genomic tools are more readily available to determine participation of various neural substrates in behavior. On the other hand, additional extension of a reverse translated platform to nonhuman primate species closer genetically to humans can further illustrate the robust nature of the key variables governing task performance.

Confidence in translational relevance is heightened, though never guaranteed, when observing functionally similar behavioral and pharmacological outcomes among multiple species. In this vein, although the touchscreen-based PRT was first developed for rats (Kangas et al., 2020), it was subsequently modified for marmoset monkeys (Wooldridge et al., 2021) and, most recently, mice (Luc & Kangas, 2024), as shown in Fig. 2. Cross-species continuity in task performance was confirmed by nearly identical effects of asymmetric probabilistic reinforcement schedules among rats, mice, nonhuman primates, and humans (cf. Luc et al., 2021; Luc & Kangas, 2024). Pharmacological evidence of cross species continuity was also supported by similar prohedonic efficacy and potency of ketamine in marmoset monkeys (Wooldridge et al., 2021) and rats (Jenkins et al., 2025). Here again, robust behavioral and pharmacological outcomes, bolstered by evidence of evolutionary conservation, highlight value in the PRT in particular and reverse translational approaches generally.

Conclusion

Taken together, a steadfast emphasis on the five considerations described above has potential to accelerate the validation and optimization of reverse translated methods for the development of novel treatment strategies. These considerations are not intended to be overly rigid or prescriptive. Rather, they are based on a longstanding association with rigor in behavioral science, with recent empirical progress of the PRT as an instructive exemplar. Of course, the methodology of reverse translation is far reaching beyond the PRT. Indeed, several other tasks that meet many of the factors described above have been developed to embrace behavioral complexity within the context of other probabilistic reinforcement paradigms (Kangas et al., 2022a) and the RDoC positive valence system framework more generally (Dexter et al., 2025).

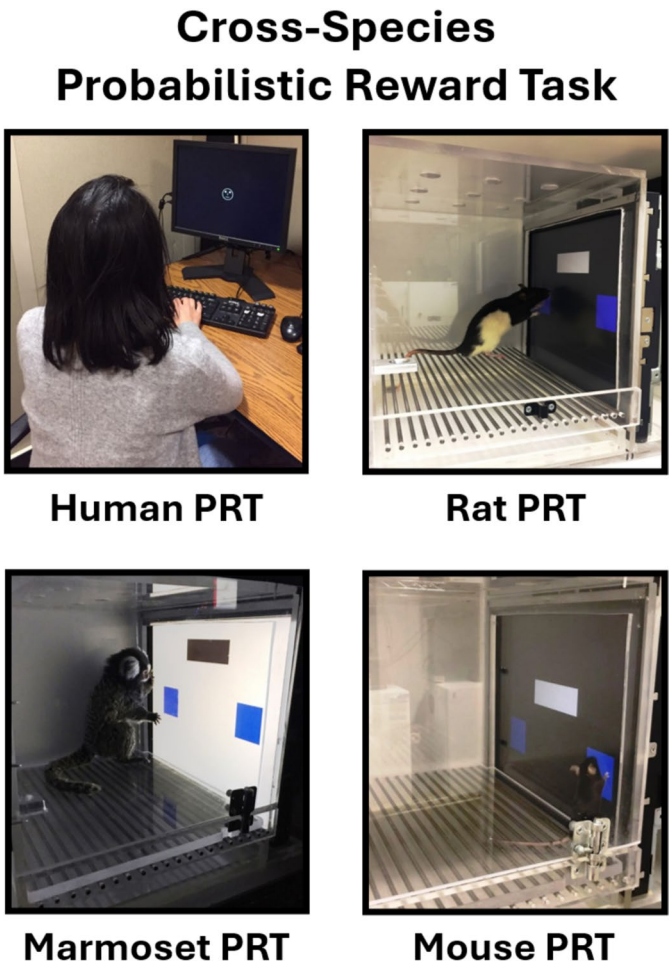

Fig. 2 Photographs of the Probabilistic Reward Task (PRT) Designed for Humans (Pizzagalli et al., 2005), Rats (Kangas et al., 2020), Marmosets (Wooldridge et al., 2021), and Mice (Luc & Kangas, 2024). *Note*. Visual discriminations are made by responding on the keyboard (humans) or blue squares (laboratory animals) depending on whether the long or short line is presented. Probabilistic reinforcement schedules are programmed such that correct responses in the presence of one line length are reinforced 60% of the time (rich), whereas correct responses in the presence of the other line length are reinforced only 20% of the time (lean)

Moreover, a growing embrace of reverse translational approaches transcends research in novel treatment strategies for anhedonia. Indeed, pursuits in reverse translation are currently active across several diverse scientific domains. For example, within the realm of substance use disorder research, Venniro et al. (2020) highlight the value of incorporating into animal models procedural features associated with effective addiction treatment strategies in humans, such as contingency management and community-reinforcement, which are sometimes ignored in preclinical research. Another creative avenue of reverse translation has

emerged in the study of multiple sclerosis and other neurodegenerative disorders, in which 't Hart (2015) argues for therapeutic strategies that fail in the clinic not be abandoned, but rather studied in animal models to understand the mechanisms responsible for their failure, which might have an added benefit of improving the animal model's predictive validity. In other studies designed to optimize neuromodulatory techniques such as deep brain stimulation for depression, Rudebeck et al. (2019) make the case for reverse translation by prioritizing brain areas that show promise in clinical patients for exploration and refinement of localization in nonhuman primates given their close homology to humans. In other work, Peleh et al. (2019) argues for more rigorous models of rodent social behavior designed to capture features of social withdrawal, based on human studies of deficits that are ubiquitous in patients with Alzheimer's disease and schizophrenia. In yet another reverse translational endeavor, Gratz et al. (2018) underscore recent advances in the ways in which computational modeling of patient data might inform how we construct better animal models of heart disease. Finally, Caudle et al. (2021) spearheaded a collection of articles that describe ways in which analgesic medications development can be enhanced by animal models that incorporate characteristics based on discoveries detailing the heterogeneity in human disease states that involve pain. Notwithstanding these varied topics, in each case, the call for and implementation of reverse translated techniques were expressly born of necessity following some period of unproductive dormancy within the respective domain.

In summary, forward translational approaches of identifying behavioral phenotypes in laboratory animals that are predictive of outcomes in human subjects have resulted in numerous biomedical advances. However, stagnation in drug discovery has encouraged the development of reverse translational approaches. These efforts prioritize the identification of behavioral phenotypes in clinical populations during task performance. In turn, formal and functional features are conserved in tasks modified for investigation in laboratory animals. Such coordinated bidirectional strategies between clinical and preclinical laboratories may accelerate the development of innovative therapeutics for the management of treatment-resistant depression and other neuropsychiatric illness.

Funding Preparation of this article was supported in part by grants R01-MH136052 from the National Institute of Mental Health and R01-DA047575 from the National Institute on Drug Abuse. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

Data Availability Because this is a conceptual review article, no new data are presented.

Compliance with Ethical Standards

Competing interests During the past 3 years, BDK has received sponsored research agreements from BlackThorn Therapeutics, Compass Pathways, Delix Therapeutics, Engrail Therapeutics, Neurocrine Biosciences, and Takeda Pharmaceuticals. No funding from these entities was used to support the current work.

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