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Translational In Vivo Assays in Behavioral Biology

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Abstract

The failure of preclinical research to advance successful candidate medications in psychiatry has created a paradigmatic crisis in psychiatry. The Research Domain Criteria (RDoC) initiative was designed to remedy this situation with a neuroscience-based approach that employs multimodal and cross-species in vivo methodology to increase the probability of translational findings and, consequently, drug discovery. The present review underscores the feasibility of this methodological approach by briefly reviewing, first, the use of multidimensional and cross-species methodologies in traditional behavioral pharmacology and, subsequently, the utility of this approach in contemporary neuroimaging and electrophysiology research—with a focus on the value of functionally homologous studies in nonhuman and human subjects. The final section provides a brief review of the RDoC, with a focus on the potential strengths and weaknesses of its domain-based underpinnings. Optimistically, this mechanistic and multidimensional approach in neuropsychiatric research will lead to novel therapeutics for the management of neuropsychiatric disorders.

1. INTRODUCTION

In *The Structure of Scientific Revolutions* (1), the nature of a scientific paradigm is described as a conceptual framework that, through a combination of ideas, methodologies, and best practices, guides research within a discipline until it—the paradigm—is no longer serviceable, often because it no longer accommodates key elements of the accumulated evidence. From this perspective, most neuropsychiatric paradigms that account for normative as well as non-normative behavior, whether psychodynamic, behavioral, humanistic, or cognitive, have been similarly challenged by the steady accumulation of conflicting data. This has led to a shift in scientific thinking that, based upon an ever-growing storehouse of neurobiological evidence, now strongly supports a paradigm that embraces both a prominent role for neurobiological mechanisms in behavior and a disease model for psychopathologies, especially for severe conditions such as schizophrenia, mood disorders, or autism. Yet, the development of this neuropsychiatric paradigm and the discovery of novel psychotropic medications for the management of neuropsychiatric disorders have been hampered by the slow emergence of methodological guidelines for a rational and evidence-based approach to preclinical neuropsychiatric research. Ideally, such guidelines should encourage a multimodal and multidimensional experimental approach that emphasizes functionally analogous studies across species to maximize the translatability of data obtained in laboratory animals. The present review is intended to illustrate the feasibility of this approach. Following a brief historical perspective on the current drought afflicting drug discovery in psychiatry, examples of multimodal and multidimensional studies in traditional behavioral pharmacology as well as in neuroimaging and electrophysiological (EEG) research are provided to highlight the feasibility and strength of this overall approach. Finally, the Research Domain Criteria (RDoC) initiative is discussed as the most promising paradigmatic framework within which multidimensional and highly translational neuropsychiatric research may flourish.

1.1. Golden Age of Psychopharmacology

The golden age of psychopharmacology was presaged in the late 1940s by the discovery of lithium carbonate for the management of bipolar disorder (then called manic/depressive disease). This fertile period of psychotropic drug discovery fully blossomed in the next two decades with the development of chlorpromazine and other phenothiazines for attenuating the symptoms of schizophrenia; the carbamate ester meprobamate and benzodiazepines (e.g., chlordiazepoxide and diazepam or nitrazepam) for providing anxiolytic or sedative effects; and monoamine oxidase inhibitors (e.g., iproniazid) and, later, monoamine reuptake inhibitors (e.g., imipramine) for combating depression. The introduction of novel psychotropics into clinical practice continued into the 1980s with the identification of atypical antipsychotics (e.g., clozapine) and selective serotonin reuptake inhibitors (e.g., fluoxetine) for the improved management of schizophrenia and major depression, respectively. Undeniably, serendipity and keen clinical observation, rather than rational drug design or translationally valid in vivo behavioral assays, played major roles in these medicinal breakthroughs. Nonetheless, these advances heralded the increasing dominance of biological approaches to the understanding and treatment of neuropsychiatric disorders and, importantly, the ensuing decades of neuroscientific discovery—promoted by the US National Institutes of Health's Decade of the Brain through the 1990s—that aimed to unravel the complex biology of behavior and neuropsychiatric disorders. And, of course, theories of brain function and dysfunction abounded during these decades. Initially, hypotheses regarding neuropsychiatric disorders were based on neuropharmacological mechanisms that mediated the beneficial actions of the new psychotropic drugs, as prominently exemplified by the dopamine (DA) theory of schizophrenia and the monoamine theory of depression. However, such theories did not consistently account for major features of such

complex and heterogenous disorders, and while new versions of existing medications were introduced, reasonable targets for novel drug development and, importantly, valid animal models for identifying such novel drugs were lacking. In part, this reflected the enormous and sometimes amorphous complexity of human behavior—both normative and nonnormative—that needed to, but could not, be fully captured in existing laboratory animal models. Furthermore, notwithstanding the classification scheme and its refinements presented in successive editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or *International Classification of Diseases* (ICD), the absence of firm, operational definitions of psychopathology (e.g., schizophrenia, depression, bipolar disorder) and the inability to accurately reflect features of the different pathologies in nonhuman subjects were serious obstacles to the creation of valid preclinical assays as models. These challenges were only compounded by the profound heterogeneity of DSM/ICD diagnoses, which, although representing generally reliable categories, might lack biological validity (e.g., 2, 3).

Despite these challenges, it is important to recognize that some laboratory animal models with satisfactory face validity have emerged and remain in use, for example, sucrose preference testing as a means of assaying reward sensitivity in nonhuman models of depression-related anhedonia (4) and, as discussed below, prepulse inhibition (PPI) to model sensorimotor gating deficits in schizophrenia (5, 6). Yet, biological models that are based on homology between features of psychopathology and preclinical end points in laboratory subjects remain scarce. As a consequence, preclinical testing generally has relied on pharmacologically valid in vivo assays that are based on behaviorally distinct effects of an already effective drug or its mechanism of action but that may not reflect features of the target pathology. At best, this approach can yield new drugs that are modified versions of already-existing medications, but it is not designed to reveal pharmacologically novel psychotropics, thus constraining the process of drug discovery and development. For example, drugs such as cariprazine, lumateperone, and pimavanserin that act via monoaminergic mechanisms and, over the past few years, have been approved for the treatment of psychosis are refined versions of already existing second-generation antipsychotic medications. Similarly, many recently introduced antidepressant medications are modified versions of earlier monoamine reuptake inhibitors. One major exception is the development of the noncompetitive NMDA antagonist ketamine for the management of treatment-resistant depression. Ketamine's antidepressant effects were first noted by illicit drug users in the 1970s and eventually confirmed in patients with depression several decades later (7, 8). It is interesting that, starting in the 1970s, a number of preclinical studies in laboratory animals (especially those employing stress-related models) also reported antidepressant-like effects of ketamine—a rare example of convergent preclinical and clinical findings identifying a novel antidepressant mechanism of action (9). Even in the case of ketamine, however, there is not clear homology between the features of depression that were attenuated in laboratory models and that are relieved in clinical patients.

1.2. Current Status of Psychopharmacology

Unsurprisingly, the general failure to identify and advance novel psychotropic candidates over the past two to three decades has led to growing dissatisfaction with established methodologies and a steady call for new approaches to preclinical research in psychiatry (10–12). In particular, the need for a preclinical research methodology with clear translational value and predictive validity has been increasingly recognized. While a new golden age of psychopharmacology has not emerged during this time, steady progress in the development of in vivo methodology to expand our understanding of brain structure and function nonetheless has provided new experimental tools that have revolutionized preclinical neurobiological research. The availability of optogenetics and chemogenetics, techniques with especially wide applicability (e.g., see 13–15), has facilitated research in laboratory animals to elucidate mechanisms and the circuitry of basic

central nervous system (CNS)-based functions in ongoing behavior, for example, learning, memory, executive function, and emotional response. For example, Liu et al. (16) were able to show that optogenetic reactivation of hippocampal neurons that originally had been activated during fear conditioning is sufficient to induce the conditioned behavioral response of freezing. In an impressive extension, Grella et al. (17) showed that optogenetic activation of dopaminergic neurons in the ventral tegmental area that provokes intracranial self-stimulation behavior can, of itself, serve as a reinforcing event to maintain operant behavior in mice. Together, lines of research that productively employ such powerful techniques promise to enhance our understanding of brain mechanisms and circuitry in normative behavior and how they may be altered in neuropsychiatric disorders.

Notwithstanding these advances, an overall scientific framework in which such multidimensional research efforts can be organized and directed toward a common understanding of normative psychological processes and their disturbance in neuropsychiatric disorders has been, until recently, lacking. The value of such a framework would be both conceptual and practical. Conceptually, such a framework would provide a neurobiological context for characterizing psychopathological conditions. Practically, it would provide guidelines for increasing the translational value of preclinical research, for example, by encouraging the conduct of functionally analogous multimodal studies in human and nonhuman subjects. Such a cross-species approach enhances the translational value of findings in laboratory animals (and could de-risk drug development) and has characterized behavioral pharmacology from its inception. For example, very early behavioral research operationalized the principles of contingency relationships in laboratory animals and later applied those principles and methods in the management of hospitalized patients diagnosed with psychosis (18). Other examples of multimodal in vivo research drawn from traditional behavioral pharmacology are discussed below. Additionally, recent translational work in two other contemporary disciplines in behavioral biology—neuroimaging and behavioral electrophysiology—is presented, followed by a brief review of the RDoC initiative, which is intended to provide a scientific, rather than nosological, framework for contemporary neuropsychiatric research. This framework was developed on the premise that a rational and multidimensional approach to preclinical research is most likely to expand our understanding of normative and nonnormative behavior and, by extension, neuropsychiatric disorders. Our purpose in the following sections is not to provide a comprehensive review of research findings across several disciplines but, rather, to illustrate the feasibility and translational value of multimodal and multidimensional science within a robust scientific paradigm. In doing so, we highlight the promise of this approach for advancing neuropsychiatric research and the development of novel medications for neuropsychiatric disorders.

2. BEHAVIORAL PHARMACOLOGY

Multimodal in vivo research, that is, work that combines multiple behavioral end points or a mix of behavioral and nonbehavioral end points in the same subjects or that employs functionally analogous methodology in nonhuman and human subjects, is a mainstay of behavioral pharmacology. The use of multiple experimental end points is an especially common approach in the preclinical evaluation of novel analgesics. Thus, the ability of candidate medications to produce analgesia-related antinociception and side effects (e.g., behavioral impairment or respiratory depression) can be evaluated concurrently, serving as a useful preclinical predictor of relative safety (19–21). For example, Withey et al. (22, 23) used antinociception and behavioral impairment to compare the effects of chronic treatment with the opioid partial agonist buprenorphine or the opioid antagonist naltrexone, medications that currently are used in the management of opioid use disorder. Their

data reveal that both chronic buprenorphine and chronic naltrexone greatly reduced the antinociceptive potency of morphine-like prescription opioids; however, only naltrexone also comparably reduced their potency for disrupting ongoing behavior. These findings have clear clinical implications for treating pain in people receiving treatment for opioid use disorder; that is, the therapeutic index of prescription opioids is more likely to decrease during buprenorphine than during naltrexone maintenance.

Another type of multimodal approach in behavioral pharmacology combines behavioral and nonbehavioral—for example, neurochemical, EEG, imaging—methodologies in laboratory animals—most powerfully, in the same subjects—to better understand neurobiological mechanisms that mediate the behavioral effects of psychoactive drugs. For example, the pioneering combination of microdialysis and self-administration procedures in the same individuals enabled Pettit & Justice (24, 25) to convincingly demonstrate in rats that reinforcing properties of cocaine are closely tied to its ability to release DA in the nucleus accumbens. Their data revealed that cocaine self-administration behavior could be time locked to the increased level of extracellular DA and, importantly, that increases in the unit dose of cocaine produced a corresponding increase in both cocaine intake and the extracellular concentration of accumbal DA. This multimodal approach of assaying brain neurotransmitter concentrations in behaving animals has been used by numerous investigators to study, in a detailed manner, the neurochemical means by which cocaine, heroin, and other self-administered drugs exert their reinforcing or other stimulus effects in laboratory animals (e.g., see 26–28).

The above examples illustrate how the two major types of multimodal research strategy were employed early on in traditional behavioral pharmacology in laboratory animals. The development of human behavioral pharmacology has permitted a third type of multimodal preclinical approach to in vivo research—one that employs homologous and, if possible, formally similar methodology and end points across studies in nonhuman and human subjects. In an early illustration of this approach, Fischman et al. (29) showed that antipsychotic drugs that decreased avoidance but not escape behavior in conditioned avoidance procedures, which were commonly used to identify antipsychotic drugs in laboratory animals, had similar effects in a variant of that procedure in human subjects. A more contemporaneous approach to the development of antipsychotic drugs is based on the observation of deficits in pre-pulse inhibition in individuals with schizophrenia, that is, the attenuation of a startle response to a loud tone by prior exposure to a milder tone. In the laboratory, DA agonists (e.g., apomorphine) and *N*-methyl-D-aspartate receptor (NMDAR) antagonists (e.g., ketamine) have been used to produce this type of sensorimotor deficit pharmacologically as a means for evaluating candidate antipsychotic drugs (30; but see 31). Depending on the drug used to produce the deficit in pre-pulse inhibition, there is surprisingly good concordance in the effectiveness with which different antipsychotic drugs reduce this deficit in both human and nonhuman subjects (6, 32). The evidence of such deficits in humans and in nonhuman subjects treated with mechanistically selective drugs supports the idea of common top-down deficits in sensorimotor gating across species (for a review, see 33) and further strengthens the translational value of this methodology in laboratory animals.

Final examples of cross-species correspondence point to the possibility of assessing end points that are reported by or are evident in human subjects but are not easily defined in nonhuman subjects. For example, the subjective effects of a psychoactive drug can be expressed by human subjects but are difficult to define in laboratory animals. One approach to this problem has capitalized on operant drug discrimination methodology in human and nonhuman subjects, showing that psychoactive drugs, for example, opioids or psychomotor stimulants, generally produce pharmacologically similar discriminative-stimulus effects across species (34). Moreover, the subjective effects of drugs in human subjects can be related to their discriminative-stimulus

effects—a correspondence that can be exploited in preclinical drug discovery and development (35). For example, morphine-like opioids have similar discriminative-stimulus effects in both human and nonhuman subjects and well-characterized subjective effects in human subjects (36). Thus, a novel drug that is discriminated as a morphine-like opioid in laboratory animals may be presumed, at least at first pass, to have morphine-like subjective effects in human subjects. In addition to its utility in preclinical drug development, this now-traditional approach in behavioral pharmacology has been a mainstay in research to establish cross-species correspondence in the subjective effects of psychoactive drugs that are currently used for either medicinal or recreational purposes. However, while acknowledging the pharmacological rigor of drug discrimination methodology and its value for cross-species correspondence in characterizing a complex behavioral end point, one must also acknowledge that it provides data only for the inference of a drug's subjective effects rather than direct evidence of those effects.

A different approach to the problem of cross-species correspondence in behavioral pharmacology comes with recent developments in the analysis of nonconditioned and naturalistic or ethologically relevant behaviors (i.e., ethopharmacology). The category is broad, including both individual behavior and group, that is, social, behavior, and encompasses a wide range of complexity. For example, the effects of drugs on the amount of motoric activity or the frequency of agonistic, that is, aggressive, display usually can be readily measured, whereas facial expressions that connote mood are less easily quantifiable. Such observation-based investigation has yielded striking examples of correspondence in the effects of drugs in human and nonhuman subjects, ranging from changes in reflexive or nonconditioned behavior of individuals [e.g., increased eye blinking or catalepsy produced by, respectively, DA agonists or antagonists (37, 38)] to increases in affiliative behavior produced by entactogens such as 3,4-methylene dioxymethamphetamine [MDMA (39)]. Historically, this has been a rich but methodologically constrained area of behavioral pharmacology in nonhuman subjects, usually requiring intensive training for the accurate scoring of behavior, either in real time or on videotape, followed by laborious analysis of relatively large data sets. More recently, however, there has been a sea change in methodology that already is reshaping this area of pharmacological research. Thus, the ever-expanding use of mobile technology to record continuous real-time data in human subjects and the availability of sophisticated software for the analysis of large data sets in both nonhuman and human subjects have provided fresh and exciting options for measuring, monitoring, and modeling behavior across naturalistic and basic research settings (40). These efforts will likely increase our ability to establish cross-species correspondence in the behavioral effects of drugs that are otherwise difficult to study. For example, video and computer vision to automatically code observable complex behavior—such as facial expressions and postural dynamics—for quantitative analysis and categorization potentially will be extremely valuable for cataloging cross-species commonalities in meaning or emotional state as well as in the effects of psychoactive drugs (41). Such advances in observational or ethopharmacological methodology, fueled by the availability of new technologies to establish and analyze robust data infrastructures, have made this an extremely promising area of current behavioral pharmacology.

The above overview and examples are meant to illustrate the rich and continuing tradition of multimodal research in behavioral pharmacology. The particular approach, for example, employing different behavioral or both behavioral and nonbehavioral end points, depends on the research question. However, regardless of the particular research methodology and behavioral or physiological end points, it is clear that the ability to replicate laboratory animal data in functionally analogous or even formally similar studies in human subjects provides an important translational advantage and, as discussed below, realizes a major goal of the RDoC approach to neuropsychiatric research. While functionally analogous studies in laboratory animals and human subjects are not

always possible, the following sections present work drawn from two areas of current preclinical research, neuroimaging and electrophysiology, in which a multimodal approach across laboratory animal and human subjects is indeed tenable and can yield highly promising translational results.

3. BEHAVIORAL NEUROIMAGING

As discussed above, preclinical in vivo models for the study of neuropsychiatric disorders are, in some cases, highly translational, particularly when functionally analogous studies can be conducted in both nonhuman and human subjects. However, there are many neuropsychiatric disorders in which the complexity of human behavior cannot be fully captured in animal models of the disease state. Another approach to understanding neuropsychiatric disorders has involved the noninvasive identification of features of neural activity and circuitry with which normative and nonnormative behavior may be associated. The neuroimaging modalities used in this approach, for example, magnetic resonance imaging (MRI) and positron emission tomography, which already have been employed in preclinical studies to uncover neural, pharmacological, and physiological changes associated with particular pathologies, are being employed to better understand commonalities in the organization and function of the brain across nonhuman and human species. This information undoubtedly will be valuable in the further development of preclinical models of neuropsychiatric disorders. For example, preclinical neuroimaging studies have helped define the receptor mechanisms engaged by novel drugs and to determine the level of target engagement needed to produce drug-induced changes that are therapeutic (42). Furthermore, many of the same neuroimaging measures can be used across preclinical and clinical studies, permitting reverse translation from clinical findings to help refine preclinical analyses (43). Taken together, these types of analyses have already demonstrated considerable overlap in brain structure and functional networks across species. Finally, and from a practical standpoint, neuroimaging techniques can also optimize CNS drug discovery by providing a metric to increase confidence in early decision making, reduce risk and costs associated with failed clinical trials, and improve success rates. Some of the MRI-based techniques that have been employed in nonhuman and human subjects are briefly discussed in the following sections.

3.1. Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) has offered an unparalleled view of brain activation and functional connectivity between different brain regions. It has also revealed critical information about brain topology (44) and how that topological organization is modified by experimental manipulations (45) and disease states (46–49) and across the life span (50, 51). Directly relevant here, some of these modifications have been demonstrated across species (52), and a number of behavioral tasks to evaluate them during neuroimaging also have been conducted across species.

However, the possibility that different species attend to different stimuli within a task may introduce high levels of species-related variability, making the results of task-based fMRI difficult to translate. In contrast, resting-state functional magnetic resonance imaging (rsfMRI) is a technique used to map functional coupling between brain regions inferred from the degree of temporal correlations between spontaneous low-frequency fluctuations in the blood oxygen level–dependent (BOLD) signal occurring in the absence of an explicit task (53, 54). Furthermore, rsfMRI is a particularly useful translational tool because it can provide valuable information about the brain in a relatively short period of time, with good internal reliability especially when using multi-echo imaging (55). The short scan session reduces the length of time a subject is required to remain motionless to avoid compromising the data quality, which is particularly desirable when conducting studies in nonhuman subjects. Investigations using rsfMRI have revealed multiple large-scale

brain functional resting-state networks (RSNs) (54, 56) hypothesized to underlie a variety of behavioral and cognitive domains (57–60). One of the hallmarks of using RSNs as end points is their reproducibility, both within and between subjects (60, 61). The stability and reproducibility of RSNs have led to the hypothesis that they may be useful as candidate biomarkers for neurological and neuropsychiatric disorders (46, 62–66). For example, alterations in RSNs have been described in autism (67), schizophrenia (62), attention deficit hyperactivity disorder (68), depression (46), anxiety (69), and substance use disorder (47–49), demonstrating their potential value as objective biomarkers for diagnosis and prognosis across a wide range of neuropsychiatric illnesses (70).

Following several influential publications demonstrating RSNs in rodents (71–74), it was noted that, as in humans, rodent brain-behavior relationships result from interactions between large-scale networks rather than individual regions of interest acting alone. The demonstration of such functional similarity has led to more in-depth investigation of the biological underpinnings of these large-scale networks, which includes interventional and controlled experiments that are not possible in human subjects. For example, in relatively recent work, MRI techniques have been combined with more invasive procedures such as tracer injections to reveal mesoscale connectivity (75), fiber-optic brain implants to collect simultaneous calcium channel recordings (76), and in vivo modulation of specific target neuron activity using optogenetics (77).

3.2. Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an alternative MRI-based technique that offers a representation of brain structure by mapping white matter connections. DTI is a flexible tool that can be used to provide information regarding normal white matter connections or gross malformations in brain volume and morphology, and it can also elucidate subtle alterations in brain connectivity and organization (78). DTI modalities have demonstrated alterations in white matter connections in humans presenting with numerous neurodevelopmental and neuropsychiatric disorders (79). Changes have been shown in measures such as regional volume, fractional anisotropy, diffusivity (including mean, axial, and radial), deformation field analysis, connectivity within and between regions of interest (including tractography and connectivity maps), and cortical thickness analysis (80–83).

DTI also has considerable translational potential, given the overlap in major white matter tracts between species (84–88) and the recent advances in high-field imaging offering improved signal-to-noise ratios and resolution compared to traditional low-field systems. However, it is important to also recognize the obstacles to conducting cross-species DTI-based comparisons. Some of these challenges are related to methodological biases and limitations, particularly in the translatability of tractography-based analysis (89). To maximize their translational value, laboratory animal studies must be designed to focus on clinically relevant end points and developmental time points and to use carefully matched controls that may be difficult to attain in human populations.

3.3. Behavior and Neuroimaging

Recently, there has been substantial interest in combining neuroimaging end points with behavioral pharmacology. Unlike EEG, which is reviewed below, MRI requires complete immobilization of the subject to obtain artifact-free images. Historically, this has meant that preclinical MRI studies have been conducted under anesthesia. However, this approach presents several issues in that (*a*) the anesthetic agent could interact with an experimentally delivered pharmacological agent when conducting pharmacological MRI studies (90), (*b*) anesthesia induces reductions in body temperature (91), and (*c*) the effects of anesthetic agents alone on RSNs and BOLD responses have not yet been fully elucidated. Collectively, these issues could introduce unknown

variables and hamper both conclusions and the translatability of MRI data between human and nonhuman subjects. To this end, several researchers over the past two decades have explored multiple options to achieve immobility in the absence of anesthetic agents, including head fixation (92) and extensive behavioral conditioning techniques (93). Notably, these efforts have met with some success, and there have been MRI studies in awake and behaving nonhuman subjects [e.g., in nonhuman primates (94)]. Clearly, this type of approach, while arduous, provides unique advantages (including obtaining behavioral and neuroimaging data within the same subject within the same experimental session) and likely will become more common as its methodology is refined.

Critically, preclinical MRI also shows promise for modeling human normative and nonnormative conditions, as many of the core functional RSNs that have been identified in humans (54, 56) have also been identified in nonhuman species (95, 96), including nonhuman primates (97–101) and rodents (102, 103). Thus, it is highly conceivable that changes in the activity of selected RSNs could serve as biomarkers for pathological conditions or, alternatively, as indicators of target engagement. With applications like these in mind, it seems that preclinical MRI is poised to become a reliable and translatable means to answer specific scientific questions related to RSNs and their interactivity. When combined with behavioral tasks or assessments, this should be a profitable line for future investigations into the neural and behavioral correlates involved in certain neuropsychiatric disorders.

4. BEHAVIORAL ELECTROPHYSIOLOGY

In recent years, there has been increasing interest in using EEG end points in behavioral pharmacology. The electroencephalogram, recorded during either resting (task-free) states or tasks [giving rise to event-related potentials (ERPs)], offers several advantages for cross-species integration (for recent reviews, see 104–106). First, unlike fMRI, EEG recordings across species can be accomplished with freely behaving (i.e., physically unconstrained) animals. Second, due to their high temporal resolution (in the millisecond range), EEG recordings allow for the disentangling of different oscillatory patterns (EEG frequency bands) that have been associated with different functions and neural generators (105, 107). In particular, spectral decomposition or time-frequency analyses, which have been hypothesized to index local circuitry activity implicated in specific neural computations, hold particular promise for elucidating underlying neural mechanisms, especially as brain oscillations have been remarkably preserved across evolution (108).

Recent studies using time-frequency analyses in conjunction with complex tasks that are functionally analogous across species have yielded results that are consistent with this assumption. Thus, several groups have reported similar oscillatory patterns across species, including increased frontal theta oscillations when rats and humans processed incongruent or erroneous information (109, 110), increased frontal midline delta-band power in response to unexpected reward in humans and mice (111), and pain-induced gamma-band oscillations in both humans and rodents (112). Critically, EEG studies using optogenetics to drive the oscillations under investigation (e.g., pain-induced gamma oscillations) established that such oscillations causally affected the construct of interest [e.g., pain perception (113)]. These time-frequency analyses have been complemented by analyses in the time domain (i.e., ERPs). These have shown similar error-related negativity approximately 100 ms after macaques and humans committed errors in speeded reaction time tasks (for a review, see 114) and feedback-related negativity in response to reward feedback in the anterior cingulate cortex (115). As shown in **Figure 1**, the latter effects mirror human source-localized EEG findings obtained using the same probabilistic reward task (116).

Third, and particularly relevant here, EEG recordings can be easily coupled with pharmacological challenges, with their translational utility boosted by demonstrating similar drug effects across species. For example, the mismatch negativity and underlying theta oscillations have been

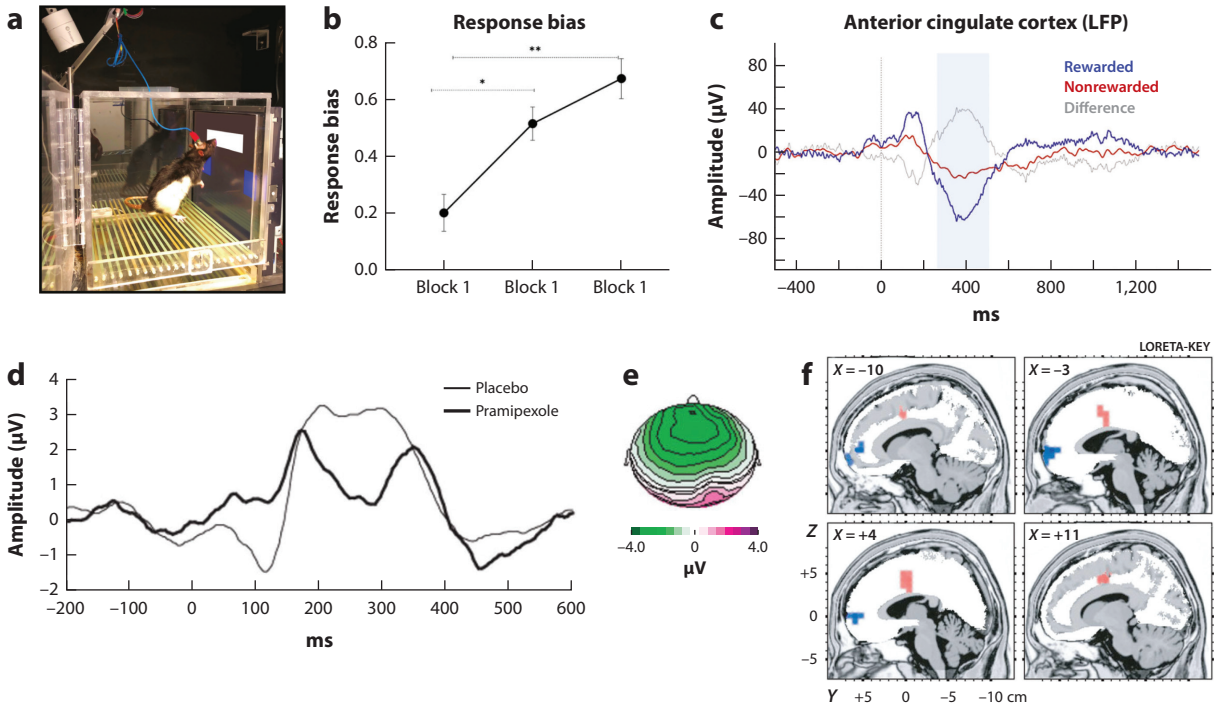

Figure 1

Cross-species electrophysiological assays of reward learning. (*a*) Electrophysiological recording setup of a rat performing a touch screen–based probabilistic reward task (PRT) that has been back-translated from humans to rats. (*b*) In a study using two difficult-to-discriminate stimuli (here, a long versus short line) that are paired with a differential reinforcement schedule, rats (and humans, not shown) rapidly develop a response bias in favor of the more frequently rewarded stimulus. (*c*) In rats, feedback-locked event-related potentials can be recorded at a local field potential (LFP) electrode placed in the cingulate cortex [anterior-posterior (AP): +1.2; medial-lateral (ML): +0.8; dorsal-ventral (DV): −3.0] in response to rewarded (*blue*) and nonrewarded (*red*) trials. Gray indicates the difference between blue and red waveforms. (*d*) In humans performing the PRT, similar feedback-related waveforms are recorded in response to rewarded stimuli. Notably, a pharmacological challenge hypothesized to decrease dopaminergic signaling (0.5 mg of the D2/3 agonist pramipexole) due to presynaptic autoreceptor activation was associated with blunted feedback-related positivity. (*e*) Topographic map of the feedback-related negativity (FRN) difference wave (pramipexole minus placebo). (*f*) Voxelwise difference in current source density in response to reward feedback. Red indicates that placebo produced a greater response than pramipexole, and blue indicates that placebo produced a poorer response than pramipexole. The statistical map was thresholded at $p < 0.005$. Panels *a*–*c* adapted from Reference 115, and panels *d* and *e* adapted from Reference 132.

found to be sensitive to NMDAR antagonists (e.g., ketamine, phencyclidine) in mice (117), nonhuman primates (118), and humans (119). Similarly, cross-species studies of event-related oscillations have revealed reduced phase locking between frontal and parietal electrodes in the theta frequencies for humans and rats with a history of adolescent alcohol exposure (120), raising the possibility that alcohol exposure during adolescence results in reduced coupling among cortical neuronal networks. Moreover, allopregnanolone, which was recently approved by the US Food and Drug Administration for the treatment of postpartum depression, has been shown to increase theta and beta power in both humans and rats (121). Finally, D-amphetamine was found to increase ERPs elicited by reward feedback in both humans and mice (122), whereas only humans showed the expected pharmacological modulations in reward-related delta oscillations.

Notwithstanding the many similarities in drug effects between human and nonhuman species that are listed above, the last null findings highlight some of the caveats that must attend

cross-species pharmacological EEG studies. First, there are uncertainties about how human EEG frequency bands mirror those in rodents. For example, a recent study comparing resting-state EEG between humans and rats found that, relative to the eyes-open condition, the eyes-closed condition was associated with higher power at 8–12 Hz and 18–22 Hz at occipital electrodes as well as lower power at 18–22 Hz and 30–100 Hz at frontal electrodes in humans (123). Conversely, in rats, the eyes-closed condition was linked to higher power at 1–4 Hz, 8–12 Hz, and 13–17 Hz in the frontal-central region. Second, cross-species homology is unclear, especially for cortical regions. Third, there are cross-species differences in task experiences, including overtraining in rodents versus a novel experience for humans or performing the task in mildly food-deprived experimental animals versus humans who are not food deprived or even satiated. Finally, there are often marked differences in the types of rewards used, including use of primary reinforcement (e.g., food) in experimental animals versus use of secondary (e.g., money) or social (e.g., desire to perform well) reinforcement in humans. Notwithstanding these caveats and the experimental challenges they illustrate, EEG recordings across species have substantial translational potential for accelerating evaluation, optimization, and prioritization of candidate compounds.

5. THE RESEARCH DOMAIN CRITERIA FRAMEWORK

The DSM and ICD systems are regularly updated and widely accepted nosologies that provide symptom-based and clinically valuable diagnostic classifications of neuropsychiatric disorders. However, as discussed above, preclinical efforts to identify and advance novel psychotropic candidates have been highly unsuccessful in recent decades, bringing the utility of DSM- or ICD-based diagnostic criteria in guiding preclinical efforts in neuropsychiatric research and drug discovery into question. Such considerations led to a major National Institute of Mental Health–sponsored effort to develop a new, rational framework for preclinical neuropsychiatric research and drug discovery based on RDoC (3, 124). Unlike the DSM and ICD systems, the RDoC framework rests firmly—though not exclusively—on a neurobiological foundation based on preclinical research in laboratory animals, as well as the key role of target engagement. By focusing on fundamental dimensions of behaviors that can be studied in animals, RDoC provides an ideal framework for translational research. Reflecting the current state of our understanding, the RDoC matrix currently defines six different functional domains that play a role in normative and, presumably, nonnormative behavior: negative valence systems, positive valence systems, cognitive systems, arousal/regulatory systems, sensorimotor systems, and systems for social processes. In essence, this approach embraces a full range of biologically relevant methodologies and multiple units of analysis—from genetic and molecular to behavioral and self-report—to foster a multimodal assessment of neuropsychiatric disorders, with a strong emphasis on functionally analogous end points across human and nonhuman species. As a consequence of this emphasis, the RDoC approach also encourages reverse translation when necessary to develop analogous assays in human and nonhuman subjects. Although the orientation of the RDoC framework is heavily neurobiological, its domain-based approach additionally acknowledges the role of neurodevelopmental and environmental influences on our understanding of biobehavioral science and in the continual reshaping of these domains (for recent reviews, see 125–127).

Notwithstanding its strengths, the RDoC initiative has also received criticism. It can appear to prioritize an understanding of neural circuitry and neurobiological mechanisms in normative and nonnormative behavior. However, as has been stressed by proponents of the RDoC approach (128), a fundamental tenet of the framework is that all units of analysis, including self-report and behavior, are of equal value. Accordingly, in the RDoC approach, neuropsychiatric disorders can be studied simultaneously through quantifiable observed behavior as well as with neurobiological

data. Another criticism that deserves mention is that the nonnormative behaviors that characterize the most severe neuropsychiatric disorders (e.g., schizophrenia, bipolar disorder, autism) may not be on the same dimensional continua as normative behavior—a fundamental assumption of the RDoC approach—but instead reflect qualitatively different states (129). Thus, according to this criticism, the domain-based framework that constitutes the RDoC may be relevant to normal brain function but not to disease states that are better explained within a disease model. Critics also point out that, as our understanding of brain function is still limited, a focus on currently well-established brain pathways and mechanisms may be shortsighted, thereby neglecting emerging neurobiological targets (130). While both the latter criticisms (the view of psychopathology and normative behavior on different continua and overreliance on currently established neurobiological mechanisms) deserve attention, it is important to keep in mind that the RDoC framework provides a set of dynamic principles that allow great flexibility in building and refining the RDoC matrix. It is to be expected that, as our knowledge base grows, the matrix will evolve to better reflect our improved understanding of neuropsychiatric disorders, which in turn should have important treatment implications.

Ultimately, the future value of the RDoC approach will be measured by its clinical utility as well as by the development of novel psychotherapeutic drugs. In this regard, findings from a recent multisite study provide evidence that leveraging individual differences in fundamental dimensions of behaviors may be useful for guiding treatment decisions. Accordingly, Ang et al. (131) recently reported that, among a large sample of individuals with major depressive disorder, individual differences in reward learning abilities and resting-state functional connectivity within the nodes of the brain reward system (the nucleus accumbens and rostral anterior cingulate cortex) predicted response to the atypical antidepressant bupropion after failing eight weeks treatment with the first-line treatment sertraline (a serotonin reuptake inhibitor). Of note, no baseline clinical features predicted such outcome. Findings such as these bolster the view that objectively quantifiable and granular assessments of fundamental dimensions of behavior, which have been linked to brain mechanisms, can provide key insights toward personalized treatments.

Overall, the RDoC initiative has provided a rational way forward to provide a robust framework for preclinical neuropsychiatric research and, by extension, to address the poor record of neuropsychiatric drug discovery over the past several decades. It seems intuitive that this research strategy—employing multimodal and cross-species methodologies and oriented toward the development of reliable and valid biomarkers and target engagement—will pay great dividends. Optimistically, this emphatically translational approach to neuropsychiatric research will greatly illuminate our understanding of neuropsychiatric disorders and reveal novel avenues of drug discovery for their management.

6. CONCLUSION

The development of the RDoC as an organizing yet flexible framework for preclinical research has been a major development in the current paradigm of biological psychiatry. The emphasis on neurobiological target engagement using multimodal in vivo methodology across nonhuman and human subjects suggests that the RDoC provides a means for optimizing the translational value of preclinical neuropsychiatric research. As described in the previous sections, the use of multimodal and cross-species methodology has a rich history in behavioral pharmacology and currently is employed in exciting avenues of investigation in other disciplines within behavioral biology, including electrophysiology and MRI. To accelerate the development of novel and more efficacious treatments there are important priorities that will need to be pursued in future studies. First, as summarized across sections of this review, the use of functionally identical methods

across species appears imperative in order to accelerate translation. Lead compounds could be prioritized based on their ability to modify a functional domain in experimental animals (e.g., reward learning while pursuing development of antianhedonic compounds, cognitive control while pursuing procognitive compounds). Second, studies across species, including Phase I/II trials in humans, should include direct testing of target engagement consistent with an experimental therapeutics approach. Third, studies across species should evaluate the psychometrics of variables under investigation (e.g., internal reliability, test-retest reliability), which represents a necessary step toward replication and generalization. Finally, and as exemplified in several findings reported here, the search for new therapeutics for neuropsychiatric disorders will necessitate collaborations across disciplines, laboratories, and academia/industry. Hopefully, the application of a mechanistic and multidimensional approach in neuropsychiatric research will continue to expand and, through highly translational research findings, reveal novel avenues of drug discovery for treating neuropsychiatric disorders.

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