Translational Behavioral Pharmacology: The Utility of Preclinical Models

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For over 70 years, the field of behavioral pharmacology has contributed significantly to our understanding of relationships among behavioral processes, environmental context, and drug action. Since its inception, behavioral pharmacologists have maintained a focus on characterizing drug effects to inform both the recreational and therapeutic consequences of consuming psychoactive substances. As both stubborn public health concerns persist and new challenges arise, behavioral pharmacology has evolved to prioritize translational relevance. This chapter provides a brief review of this evolution.

The first section includes a historical sketch of behavioral pharmacology's origin and fortuitous intersection with the emerging science of operant conditioning to develop *assays*. Within this context, assays refer to behavioral techniques based on schedule-controlled responding, drug self-administration, and drug discrimination, designed to reveal fundamental pharmacological properties when drugs serve as antecedents or consequences of operant behavior.

The second section reviews how behavioral pharmacology capitalized on progress in the field of animal cognition to construct laboratory *models*. Here, models refer to more complex arrangements of operant contingencies designed to capture elements of animal behavior as translationally relevant predictors of the human drug experience to determine the safety and efficacy of candidate pharmacotherapeutics. Put another way, assays are direct assessments of drug action when they are antecedents or consequences of behavior, whereas models are designed to provide representations of drug effects on more complex behavioral processes that require interpretive caution and rigorous empirical validation to confirm translational relevance. Behavioral pharmacology's longstanding and ever-evolving translational approach in preclinical research has positioned it advantageously to contribute to both lingering and new public health

challenges that might be mitigated by pharmacotherapeutics for patients with unmet treatment needs.

Traditional Assays in Behavioral Pharmacology

Schedule-Controlled Responding

Seventy years ago, Dews (1955) conducted seminal work in laboratory animals that would contribute to the very definition of behavioral pharmacology by examining how drugs affected steady-state response patterns under different schedules of reinforcement. One striking feature of his early observations was that pentobarbital, a drug that was otherwise viewed as a prototypical depressant, could decrease or increase rates of responding, depending on the environmental conditions arranged. The timing of Dews' arrival at Harvard Medical School and his subsequent introduction to B. F. Skinner and his colleagues was fortuitous, as the latter group was cataloging the many functional relationships between operant behavior and various schedules of reinforcement (typified in Ferster & Skinner, 1957). This set the occasion for a productive marriage of behavior analysis and pharmacology (Dews, 1987).

These early studies by Dews and his students during the 1950s and 1960s had a major impact on the emerging field of behavioral pharmacology (Barrett, 2002). For example, the observations that the same drug could have opposite effects depending on the pattern of schedule-controlled behavior challenged longstanding pharmacological taxonomies, such as stimulants and depressants. Dews' findings demanded attention to behavioral and environmental determinants within a science of pharmacology. No longer would mechanistic explanations, based solely on receptor theory or the neurophysiological substrate of drug effects, suffice in a complete characterization of the psychoactive drug experience. A science of behavior would also be needed.

In this regard, a key consequence of early studies of drugs and schedule-controlled behavior was the emergence of unifying principles to account for these newly described effects of drugs. For example, the principle of rate dependency described how drug treatment, regardless of pharmacological mechanism, often increases the probability of low-rate behavior and decreases the probability of high-rate behavior. This was observed across diverse drug classes, schedules of reinforcement, and species (McKearney, 1981; Sanger & Blackman, 1976).

Encouraged by successes in finding order in drug action using operant behavior, subsequent work in the early days of behavioral pharmacology described other phenomena and principles with high translational relevance that could be studied by establishing schedule-controlled behavior under various conditions. Select canonical examples include the use of escape/avoidance procedures to examine anxiolytic drug effects (Geller & Seifter, 1960), the development of reinforcement-loss hypotheses within the context of behavioral tolerance (Schuster et al., 1966), and the identification of antidepressant-like effects using differential reinforcement of low rate schedules (McGuire & Seiden, 1980), to name a few. In each of these lines of work, the behavioral level of analysis allowed for a more complete characterization of drug action than would otherwise be unpredicted by studying receptor mechanisms or neural substrate alone.

Drug Self-Administration

Soon after the introduction of operant conditioning procedures within the realm of pharmacology, these methods were extended to the phenomenon of drug-taking behavior, also known as drug self-administration. Empirical study of drug self-administration can be traced back to early work by Spragg (1940) showing that opioid-dependent chimpanzees would engage in a

series of behavioral responses to obtain an injection of morphine. This landmark work provided early clues that volitional drug-taking behavior could be studied under laboratory conditions.

Rigorous assessment of the initiation and maintenance of drug self-administration, however, would require schedule-controlled behavior, paired with innovative advances in behavioral apparatus, allowing for intravenous drug administration to serve as the consequence of the subject's own operant behavior. Early studies in rats (Weeks, 1962) and rhesus monkeys (Thomson & Schuster, 1964) demonstrated the feasibility of this approach, as nonhuman subjects self-administered drugs from diverse drug classes. This research confirmed pharmacodynamic (i.e., brain receptor-mediated action) and pharmacokinetic (i.e., behavioral time course of action) features of drug-taking behavior (Deneau et al., 1969). The similarities between drug and non-drug reinforcers in the acquisition and maintenance of operant behavior were striking (Branch, 2006). Drug self-administration represented behavioral pharmacology's first truly translational enterprise.

Accumulating evidence in the early drug self-administration literature suggested a close correspondence between the drugs that laboratory animals would readily self-administer and those that humans used and abused. Researchers quickly recognized that self-administration in the nonhuman animal lab was remarkably well-suited to provide objective appraisals of the abuse potential of psychoactive drugs (Katz & Goldberg, 1988). If a drug reinforced—or failed to reinforce—nonhuman drug-seeking and drug-taking, then the same was probably true for humans. What started with the lofty search for opioid analgesics with reduced reinforcing efficacy relative to morphine (Woods et al., 1982) remains today the gold standard requirement for preclinical evaluation of a drug's reinforcing effects that contribute to its addiction liability (Ator & Griffiths, 2003). Indeed, data from these behavioral procedures are often required for Food and Drug Administration (FDA) approval of a new psychoactive drug (Mansbach et al., 2003).

Important advances in self-administration techniques have continued, expanding their translational value for assessing a drug's addiction potential. For example, a growing appreciation of schedule features (Panlilio & Goldberg, 2007; Schindler et al., 2002) and other experimental variables such as the duration of drug-access periods (short vs. long access to respond for the drug, e.g., 1-hr vs. 6-hr; Allain & Samaha, 2019) have permitted more detailed characterizations of a drug's reinforcing effects. In turn, this has encouraged consideration—beyond simply whether a drug will or will not serve as a reinforcing stimulus—of the conditions under which a drug will maintain self-administration behavior. The outcome of these approaches is a more refined analysis of its addiction potential (see *Handbook* chapter by Strickland et al. for further discussion).

The translational focus of behavioral pharmacology has also urged changes to existing self-administration methodology. For example, although intravenous drug delivery has many practical advantages in scheduling reinforcers with precision in the laboratory, this route of drug administration is uncommon for humans when taking most drugs of abuse—opioids being a notable exception. Thus, behavioral pharmacologists have explored more translationally relevant routes of administration depending on the drug of interest, for example, oral alcohol consumption (e.g., Samson & Czachowski, 2003) and vapor inhalation of cannabinoids (e.g., Nguyen et al., 2016) in nonhuman laboratory experiments.

Another change motivated by translational utility is to study drug self-administration in a choice situation, with one lever offering a drug reinforcer and a second lever arranging non-drug consequences (Bergman & Paronis, 2006). Critically, it also comports well with medication-development approaches in which delivery of the candidate therapeutic reduces responding for maladaptive reinforcers (i.e., drugs of abuse) and increases responding for adaptive non-drug consequences (Banks & Negus, 2017). For example, agonist replacement therapies for opioid use

disorder, such as buprenorphine or methadone maintenance, are medications designed to reallocate responding by reducing illicit opioid-taking and allow the patient to instead engage in other adaptive, non-drug-taking behavior.

Drug Discrimination

Behavioral pharmacology and the experimental analysis of behavior continued to mature during the 1960s and 1970s, and the value of studying drugs as reinforcers of operant behavior became obvious. In turn, parallel investigations examining drugs as antecedents of operant behavior, via their discriminative stimulus functions, would similarly bear fruit with comparable translational importance. Like drug self-administration, drug discrimination has historical precursors in studies of antecedent stimulus control. For example, investigations of state-dependent learning (Girden & Culler, 1937), which focused on conditioning and memorial processes, often included drug states as the variable of interest (Overton, 1964).

During the same era, the psychophysics of stimulus control using exteroceptive cues like chamber lights revealed exquisite order in operant responding (Blough, 1967). This begged the question of whether moving the stimulus from outside the animal to inside, via drug treatment, could establish similar discriminative control. The answer was a resounding yes and, like drug self-administration for the study of reinforcing stimuli, drug discrimination satisfied academic pursuits by expanding the classes of discriminative stimuli available for study (Schuster et al., 1981). More importantly, however, it provided scientists with the ability to characterize the interoceptive effects of psychoactive drugs, which had previously been thought too private to study objectively (Kangas & Maguire, 2016).

In drug discrimination experiments, treatment with a biologically relevant dose of a psychoactive drug produces an interoceptive cue that serves as a discriminative stimulus through differential reinforcement. That is, in sessions following drug administration, responses on one operandum (drug lever) result in reinforcement, whereas responses on the other operandum (vehicle lever) are reinforced in sessions following administration of the drug's inert vehicle (e.g., saline). That a drug can serve as a discriminative stimulus with many of the same features and functions as exteroceptive stimuli, like chamber lights or tones, is interesting. However, what makes drug discrimination especially valuable as a translational assay in behavioral pharmacology is its ability to readily and reliably provide key pharmacological characterizations of drug action. For example, a seminal study by Shannon and Holtzman (1976) trained groups of rats to discriminate morphine versus saline. Following this relatively simple preparation, they were subsequently able to characterize receptor selectivity (i.e., identifying specific brain receptors activated by specific drugs), potency (i.e., the dose at which a behavioral effect is observed relative to other opioids), efficacy (i.e., how effective the drug is at producing maximal interoceptive effects relative to other opioids), and time course of action (i.e., how long the behavioral effects persist).

Because generalization gradients around the drug discriminative stimulus resembled those of exteroceptive discriminative stimuli, animals trained to discriminate morphine, could be tested with a novel or otherwise uncharacterized drug to determine if that drug shared interoceptive stimulus effects with morphine. The ability to assess not only morphine in this way, but a wide range of drugs and drug classes, provided translational value rivaling the benefits derived from drug self-administration (McMahon, 2015). Indeed, drug discrimination methods were so useful in appraising the similarity of interoceptive effects of new drugs, relative to those of drugs with

abuse liability, these methods are now routinely used by both the Drug Enforcement Agency (DEA) for legal scheduling under the Controlled Substances Act (Spillane & McAllister, 2003) and the FDA for approval of new medicines (US FDA, 2017).

Like schedule-controlled responding and drug self-administration, drug discrimination methods were optimized and expanded following early validation (Glennon & Young, 2011). For example, protocols emerged to train discriminations among multiple drugs (e.g., Drug A vs. Drug B vs. vehicle), which allowed for complex assessments of the interoceptive effects across multiple drug classes (Overton, 1982). Other approaches used this assay to study putative pharmacotherapeutics to substitute for the interoceptive effects of abused drugs as a laboratory surrogate for agonist replacement therapies (LeSage et al., 2009), like the buprenorphine/methadone example for opioid use disorder described above. Drug discrimination has also been used to evaluate the ability of innovative treatment strategies, such as nanoparticle-based vaccines, to attenuate or block the interoceptive effects associated with the abuse liability of the training drug (Desai & Bergman, 2015).

Finally, drug discrimination studies using antagonists as the training drug have greatly informed the study of withdrawal in drug-dependent subjects. Here, the laboratory animal is treated daily with an agonist like morphine. Under these chronic conditions, the subject is trained to respond differentially following administration of a receptor-selective antagonist designed to precipitate withdrawal, or its vehicle, which does not disrupt the interoceptive effects of the agonist. These methods allow for an objective characterization of the interoceptive phenomenon of drug withdrawal in a dependent subject, including magnitude and time course of effect (Gellert & Holtzman, 1979). An important translational direction of this approach is that it can be used to effectively characterize receptor-mediated behavioral effects associated with dependence and

evaluate the potential of pharmacotherapeutics to attenuate the aversive effects of drug withdrawal, as shown previously in subjects treated chronically with opioids (France et al., 1990), benzodiazepines (France & Gerak, 1997), and cannabinoids (Kangas et al., 2020b).

Preclinical Models in Behavioral Pharmacology

The field of behavioral pharmacology has long recognized the importance of translational research that bridges basic laboratory findings and clinical outcomes in patient populations. Although the foundational assays described in the preceding section have offered considerable insight into the behavioral, reinforcing, and discriminative stimulus properties of psychoactive drugs, they were not designed to capture the full complexity of drug effects on complex cognition-related behavior (e.g., learning, memory, attention). Moreover, contemporary challenges (e.g., the opioid epidemic, effective management of pain, the need for safe and effective medications for neuropsychiatric illness) have encouraged the emergence of models that reflect the multifaceted nature of these complex behavioral and neurobiological processes. To meet these challenges, behavioral pharmacologists have developed preclinical models designed to assess translationally relevant classes of behavior and accelerate the search for candidate medications for unmet treatment needs. The following sections review expansions of behavioral pharmacology within the context of animal modeling in preclinical research.

Measuring Pain and Analgesia

The effective management of pain remains one of the most pressing public health issues, particularly given the staggering toll of the opioid epidemic (Christie et al., 2017). Despite their efficacy in treating many painful conditions, traditional opioid analgesics pose significant risks,

including respiratory depression, abuse, and dependence. Consequently, there is critical demand for novel pharmacotherapeutic treatment strategies. To aid this search, preclinical models have emerged in behavioral pharmacology to assess analgesic properties of new drugs while concurrently examining their potential unwanted effects. The distinction between nociception and pain, along with evolving strategies to measure these processes in animal models, are central to this effort.

Nociception vs. Pain

Nociception refers to the neural processes involved in the detection of noxious or harmful stimuli, typically manifesting in reflexive autonomic responses (Dubner, 1983). While these nocifensive reflexes are useful in early analgesic screening, they do not capture the subjective or emotional experience of pain, which is inherently multidimensional (Mogil, 2009). Pain involves sensory, affective, and cognitive components, all of which shape the individual's behavioral response to, and perception of, nociceptive stimuli (Rainville et al., 1992). This conceptual distinction is especially relevant for opioid use disorder. Historically, opioids have been the first-line treatment for moderate to severe pain; however, they also engage neural pathways associated with reward, thereby increasing the risk of abuse and dependence (Kosten & George, 2002). The *holy grail* in analgesic development is thus to identify drugs that effectively reduce pain while minimizing reinforcing properties and overdose risk associated with traditional mu opioid agonists (Corbett et al., 2006). A deeper understanding of pain mechanisms—and the continued refinement of preclinical assessments—may ultimately inform the development of analgesics with reduced misuse potential. Whether this goal can be fully achieved remains an open question (Mao, 2012).

Traditional Reflex-Based Assays of Nociception

Reflex-based assays have long been a mainstay in pain research in laboratory animals (Gregory et al., 2014). Seminal methods such as the tail-flick, paw-withdrawal, and hot-plate tests measure latency to withdraw a body part from a noxious thermal stimulus. Similarly, chemical irritants (e.g., formalin) have been used to induce paw-licking, flinching, and writhing behaviors in rodents. These thermal and chemical assays, along with others using mechanical or electrical stimuli, provide rapid and highly reproducible measures of nociceptive thresholds and can be used to determine the ability of drugs to raise them (i.e., antinociceptive drug effects) in a range of species, from rodents to nonhuman primates (Le Bars et al., 2001).

Despite their relative simplicity and reliability, reflex-based models have significant limitations regarding their translational validity. First, these procedures primarily engage spinal or lower-level neural processes (Matthies & Franklin, 1992), leaving open the question of whether a tested drug truly relieves pain per se or simply dampens a reflex response. Second, interpreting the absence of a withdrawal response can be confounded by sedation, a common feature of opioid analgesics, and motor impairment, which is an outcome observed following administration of virtually every psychoactive drug at a high enough dose (Negus, 2018). As a result, these models often generate false positives for antinociception when, in fact, the outcome is merely a product of sedation, stupor, or other nonspecific motoric disruption (Withey et al., 2020).

Moreover, most reflex-based assays are not designed to capture the persistent or affective features often associated with clinically relevant pain conditions—such as neuropathic or inflammatory states. Although specialized paradigms such as nerve ligation (Rodríguez-Palma et al., 2024) or monoiodoacetate injection (Pitcher et al., 2016) are designed to induce chronic symptomatology in rodents, reflex-based methods usually measure acute nociceptive thresholds

over short durations. Consequently, although these assays remain valuable for early high-throughput screening of candidate medications, there is a clear need to supplement these models with others that incorporate the heterogeneous, cortical-dependent aspects of pain.

Translational Models of Pain

In response to the limitations of reflex-based tasks, researchers have developed translational models designed to integrate behavioral, cognitive, and motivational dimensions of pain. These models seek to measure not just the ability of a putative analgesic to induce the absence of pain-related behavior but also the *restoration of function* of adaptive operant behavior.

One illustrative approach that builds upon traditional thermal nociception assays, but avoids the pitfalls of nonspecific motoric disruption leading to false positives, arranges concurrent operant schedules of reinforcement within the experimental protocol (Withey et al., 2018). For example, a nonhuman primate responds on a lever under a fixed-ratio schedule of food reinforcement during a 10-min component. The subject is then evaluated for analgesia by measuring the latency to withdraw a shaved portion of its tail from warm water during the next 10-min component. Alternating between these components across test sessions provides the ability to systematically assess, within subject and during the same experimental session, both the antinociceptive (i.e., changes in tail-withdrawal latency) and motoric (i.e., changes in lever response rates) effects of a candidate analgesic. For example, when tested in this manner, traditional opioid analgesics reliably produce dose-related increases in tail-withdrawal latencies from warm water but also dose-dependently suppress operant responding, presumably reflecting their well-known sedative and stuporific effects.

The relative dose ranges over which these two effects occur, often expressed as a ratio of the effective dose required to produce a 50% antinociceptive effect and the effective dose to produce a 50% rate-decreasing effect (also known as ED_{50} values), can determine a drug's *preclinical therapeutic ratio*—a metric designed to quantify its antinociceptive efficacy within the context of its nonspecific behavioral disruption. This value can subsequently serve as a standard upon which to juxtapose outcomes following other candidate analgesics, indicating whether they produce analgesic-like effects with a reduced motorically disruptive profile.

Moreover, a comprehensive safety and efficacy profile can be enhanced further with other assays, including self-administration paradigms to assess abuse liability (O'Connor et al., 2011) and whole-body plethysmography to evaluate respiratory depression (Crowley et al., 2021). Although these methods are typically conducted separately from pain models, coordinated multimodal assessments in the same species and with the same drug doses can collectively provide critical information about a drug's potential for misuse or overdose. In addition to appraisals of antinociception and analgesia, this approach could move the field closer to the elusive goal of identifying analgesics with improved therapeutic windows and a reduced risk profile.

Other approaches to modeling pain and analgesia have prioritized an operant framework as the central tenet. For example, rodents (Neubert et al., 2005) or nonhuman primates (Kangas & Bergman, 2014a) can be trained under positive reinforcement contingencies to make a pain-inducing operant response for palatable food (e.g., pressing a shaved portion of their face on a heated surface [rats] or pulling down a heated thermode bar [monkeys]) under conditions in which the temperature of the thermal operandum increases across trials. The highest temperature at which an animal will still perform the operant response under the programmed reinforcement schedule is considered a functional measure of their ability to tolerate pain. If a candidate analgesic raises this

threshold, it indicates that the drug can restore operant behavior despite the presence of nociceptive stimulation. Critically, the value of this approach lies in its capacity to measure the restoration of behavior and, thus, modeling the ability of a drug to assist in getting the subject back to work in the face of otherwise painful conditions.

Other non-reflex-based animal models of pain take a more ecological approach by emphasizing the rescue of naturalistic pain-depressed rather than pain-elicited behavior. For instance, studies in mice have capitalized on their well-characterized nest-building behavior to serve as a complex, cortically mediated response that is sensitive to disruption by inflammatory or neuropathic states and can be restored by known analgesics (Jirkof et al., 2013). In these protocols, mice typically receive cotton squares or fibrous materials. Under normal conditions, mice will shred and organize such material into a coherent, bowl-shaped nest. When experiencing painful stimuli, however, nest-building quality deteriorates, and animals often leave much of the material unshredded, constructing shallow or incomplete nests. Administration of nonsteroidal anti-inflammatory drugs or low-efficacy opioids can attenuate these deficits and restore nest complexity. As such, nest-building can serve as a functional endpoint for assessing ecologically relevant analgesic efficacy rather than merely suppressing nocifensive reflexes (Negus et al., 2015). By capturing a behavior that aligns more closely with how pain disrupts daily activities in humans, these ecologically centered models highlight the potential for identifying analgesics that preserve quality of life with fewer confounding sedative or motorically disruptive effects (Negus, 2018).

Taken together, these translational models highlight a paradigm shift beyond traditional reflex-based measures, emphasizing cortical-dependent operant and other adaptive behavioral processes designed to align more closely with human pain experiences. They also emphasize the

notion that analgesia should be inferred from the restoration of behavior rather than its absence, minimizing false positives generated from the nonspecific effects inherent in sufficiently high doses of all psychoactive drugs. As public health concerns surrounding opioid misuse persist, such refined models can accelerate the discovery of drugs that provide robust pain relief with a diminished profile of sedative, respiratory depressant, or abuse-related effects.

Touchscreen-Based Cognitive Tasks

Behavioral pharmacologists have maintained longstanding interests in examining the effects of drugs on animal models of complex behavior using traditional operant conditioning chambers (Levin & Buccafusco, 2006). More recently, the development and optimization of touchscreen-based apparatus and associated cognitive tasks to examine more diverse aspects of behavior provides an unparalleled approach with exquisite translational value (Dumont et al., 2021). These approaches in rodents (Hvoslef-Eide et al., 2016) and nonhuman primates (Galbo-Thomma & Czoty, 2023) have gained traction for their procedural flexibility, capacity for within-subject test batteries, and high degree of concordance with clinical neuropsychological assessments (Palmer et al., 2021). By enabling researchers to measure learning, memory, attention, impulse control, and executive function among other constructs and within the same platform, touchscreen paradigms represent a new wave of translational relevance in preclinical testing.

One defining feature of touchscreen-based approaches is their remarkable procedural flexibility. Traditional operant chambers for rodents or nonhuman primates rely on limited cues—lights above levers, tones, or nose-poke apertures—to serve as occasion-setting or discriminative stimuli for various classes of behavior. In contrast, touchscreen systems can present a near limitless array of visual stimuli (e.g., shapes, colors, patterns, photographs, videos) with dynamic rather

than static layouts that can be altered from trial to trial or session to session. This versatility supports not only tasks targeting specific cognitive constructs but also the development of task batteries that assess multiple domains within the same experimental session or across consecutive sessions (Kangas & Bergman, 2017). By mirroring aspects of human neuropsychological assessments, touchscreen methods can improve the predictive validity of preclinical findings across species.

The procedural flexibility of a touchscreen apparatus stems from its capacity to customize visual presentations, reinforcement contingencies, and trial structures with minimal changes to hardware. For instance, a single touchscreen chamber can be programmed for a basic visual discrimination task—where a subject must select one of two stimuli for a food reward—and then seamlessly transition to a set-shifting paradigm in which the relevant stimulus dimension (e.g., color vs. shape) changes unexpectedly. Such transitions might otherwise require new physical equipment or a reconfigured operant environment if one relied on traditional apparatus. The ease of programming complex stimulus/response contingencies in touchscreen apparatus translates into higher throughput and significantly less downtime between tasks. The option to deploy multi-task batteries within a single operant setting is a transformative development in behavioral pharmacology. Historically, the study of behavior relevant to different cognitive domains (e.g., learning, memory, attention, motivation, executive function) often required specialized apparatus, making it cumbersome, expensive, and time-consuming to compile a comprehensive profile of drug effects on complex behavioral processes. By contrast, touchscreen-based systems let researchers sequence tasks in a way that allows an animal to complete several tasks in a single session. Housing multiple assessments in one platform conserves laboratory resources and adheres

to the 3Rs (replacement, reduction, and refinement), as fewer animals are needed to gather diverse behavioral and drug-action data.

In multi-task arrangements, once an animal subject learns the basic touchscreen contingencies (e.g., paw responses to illuminated images), it usually adapts rapidly to new tasks with minimal additional training. This makes it possible to conduct more experiments in the same amount of time, thereby reducing training overhead. By arranging multiple tasks in a single session or across successive days, investigators are well equipped to capture a complex behavioral repertoire upon which to assess the effects of drugs. This is critical in modern behavioral pharmacology because it is often the case that developing new medications involves improving upon the behavioral profile of existing drugs.

One example highlighting the value of touchscreen-based batteries in behavioral pharmacology is provided within the context of cannabinoid medications development for emesis and nausea. Specifically, it is well known that FDA-approved cannabinoids, such as nabilone, can attenuate the emesis and nausea that often accompanies chemotherapeutic treatments for cancer (Rock & Parker, 2016). However, it is also clear that some patients going through chemotherapy do not want the psychoactive "high" and cognition-disruptive side effects that are also associated with cannabis products (Wesnes et al., 2010). In this vein, Kangas et al. (2016) employed a touchscreen-based battery to examine a diverse array of cognition-related behavior in nonhuman primates. After training these complex behavioral repertoires, subjects were tested following administration of a variety of cannabinoids, including Δ^9-tetrahydrocannabinal (Δ^9-THC), the primary psychoactive ingredient in cannabis, and methanandamide, a metabolically stable analog of the endogenous cannabinoid, anandamide. Behavioral outcomes using a touchscreen-based battery of tasks included significant disruption following treatment with Δ^9-THC, but not

methanandamide, of learning (repeated acquisition; Harlow, 1949), cognitive flexibility (discrimination reversal; Kangas & Bergman, 2014b), short-term memory (delayed matching-to-sample; Blough, 1959), and attention (psychomotor vigilance; Mackworth, 1948), but not motivation (progressive ratio; Hodos, 1961). Subsequent studies examining the antiemetic ability of Δ^9-THC and methanandamide in nonhuman primates observed the ability of both drugs to attenuate emetic responses to various toxins (Wooldridge et al., 2020). Importantly, methanandamide had reduced antiemetic efficacy (i.e., a lower maximum possible effect) relative to Δ^9-THC. However, methanandamide's lack of cognitive disruption across a battery of touchscreen-based tasks suggest that trading some efficacy for a more desirable overall therapeutic profile may be a rational antiemetic treatment strategy for those that would like to avoid the cognition-disruptive effects and high that are associated with traditional cannabinoids such as Δ^9-THC and nabilone. More generally, these studies typify the value in drug development of identifying relative efficacy in both the desirable and undesirable behavioral outcomes of existing medications and candidate therapeutics via touchscreen-based methodology.

Reverse-Translational Approaches in Medications Development

Behavioral pharmacology has capitalized on advances in operant theory and innovative technological development to evaluate drug effects on elements of animal behavior that are translationally relevant to the human drug experience. These assessments have been critical to preclinical evaluations of drug safety and efficacy. Recent approaches in behavioral pharmacology seek to extend this approach by emphasizing another direction in the translational loop. That is, instead of designing studies to examine elements of animal behavior predictive of the human experience, *reverse-translational approaches* focus on identifying effective tasks originally

developed for studies in human subjects and then modifying them as needed for laboratory animals. By doing so, researchers can isolate the behavioral and neurobiological underpinnings of performance change and generate direct human–animal comparisons. This often offers new insights into how specific drugs influence complex behavioral processes and ultimately fosters bidirectional alignment between human and nonhuman animal studies of drug action.

Reverse-Translating Tasks Across Species

As touchscreen-based and other computerized assessments have become more sophisticated in recent years, it has become feasible to align approaches used in the clinic to characterize behavioral phenotypes associated with human neuropsychiatric illness with analogs of animal behavior. Perhaps the first successful venture using this framework can be traced back to the Cambridge Neuropsychological Test Automated Battery (CANTAB). This array of computerized tasks is routinely used in clinical research to gauge a variety of complex behavioral and cognitive processes associated with neuropsychiatric illness (Sahakian & Owen, 1992), aging and dementia (Robbins et al., 1994), and pediatric psychological phenomena (Luciana, 2003), to name a few. As the value of these advances in cognitive testing across clinical populations became obvious, the CANTAB tasks were modified and sometimes simplified to ask similar experimental questions within the context of preclinical research in rhesus macaques (Weed et al., 1999), often yielding highly similar functional outcomes between human and nonhuman primates (Nagahara et al., 2010). Smaller apparatus and associated cognitive tasks would be developed for marmosets (Spinelli et al., 2004), squirrel monkeys (Kangas & Bergman, 2012), and rodents (Bussey et al., 2008) using CANTAB hardware and software or customized do-it-yourself approaches (Kangas & Bergman, 2017).

Recreating clinical methods in the laboratory enables important cross-species comparisons of drug effects on behavior. For example, a candidate medication that disrupts rodent or monkey performance might pose similar cognitive risks in humans. Conversely, if drug treatment produces minimal impairment in the animal version of a validated test, it strengthens the rationale for human trials, reflecting the utility of reverse-translated models (Kangas, 2022). Additionally, after establishing and optimizing correspondence between test conditions for humans and laboratory animals, invasive questions impossible to evaluate in a controlled manner in human subjects can be addressed. For example, do subjects that are particularly susceptible to self-administer drugs of abuse have inferior cognitive task performance, or do they exhibit inferior cognitive task performance because of their propensity to self-administer drugs of abuse? Such questions were recently investigated in rhesus monkeys and cocaine using CANTAB methodology paired with intravenous self-administration (Allen et al., 2024).

Beyond the diverse array of CANTAB tasks, other more targeted cognitive paradigms have been reverse-translated from methods used in human studies that have proven to be particularly useful for clinical assessment. One example, the Flanker task (Eriksen & Eriksen, 1974), is a gold standard assessment of cognitive control. In this computerized task, subjects are instructed to quickly make one of two responses on a keypad depending on a target stimulus presented in the center of the screen. For example, if < is presented, press the left response key, and if > is presented, press the right response key. Next, during test sessions, select trials are presented in which the centered target stimulus is flanked on the left and right with congruent stimuli (< < < < <). In other trials, target stimuli are flanked with incongruent stimuli (> > < > >). Presenting incongruent flankers often results in lower accuracies relative to congruent trial types, which is thought to reflect an *interference* effect. Critically, in the context of clinical assessment, these interference

effects are observed in healthy subjects but are exacerbated in those with neuropsychiatric conditions characterized by deficits in cognitive control, including attention deficit hyperactivity disorder (Mullane et al., 2009), bipolar disorder (Patino et al., 2013), depression (Pizzagalli et al., 2006), Parkinson's disease (Wylie et al., 2009), post-traumatic stress disorder (Zinchenko et al., 2017), and substance use disorders (Franken et al., 2007).

Given this ubiquity across disorders, Flanker models of cognitive control were developed for rats, for example, using nose-poke apertures (Meier & Reinagel, 2013) or touchscreen responses (Robble et al., 2021). These adaptations necessitated innovative approaches in the arrangement of visual stimuli, as the rodent's poor visual system did not permit the use of visual stimuli commonly used in human subjects (Kangas et al., 2021). Such species-specific challenges highlight the need for creativity and flexibility during the development of reverse-translational approaches. After empirical validation, however, coordinated and bidirectional studies of behavioral and drug effects on indices of cognitive control are well positioned between human subjects and laboratory animals. For example, as documented recently using the touchscreen Flanker task, Linton et al. (2024) observed nearly identical interference effects in humans and rats and an inability in both species of the putative attention enhancer, methylphenidate, to attenuate the behavioral effects of incongruent flankers.

A second prominent example of reverse-translation is provided by the probabilistic reward task. This task was designed by Pizzagalli et al. (2005) to quantify reward responsiveness—a behavioral phenotype closely associated with anhedonia. *Anhedonia*, the loss of pleasure or lack of reactivity to previously reinforcing stimuli, is commonly implicated in major depressive disorder and other neuropsychiatric conditions as well, including PTSD, schizophrenia, bipolar disorder, and substance use disorders (Der-Avakian & Markou, 2012). Derived from signal

detection theory (Luc et al., 2021), the probabilistic reward task requires human subjects to make rapid visual discriminations (long versus short line length) in which correct discriminative responses in the presence of one line length (rich stimulus) are probabilistically reinforced more often than correct responses to the other line length (lean stimulus). Under these conditions, healthy subjects readily develop an adaptive response bias toward the rich stimulus, whereas those with deficits in reward responsiveness display a blunted response bias (Kangas et al., 2022a). These deficits in task performance are correlated with anhedonia across diverse patient populations with psychiatric illness (Fletcher et al., 2015).

Given the remarkable ability of this task to objectively quantify anhedonic phenotypes, including supplemental measures to appraise candidate medications designed for patient populations that are resistant to conventional antidepressants (Pizzagalli et al., 2020), the probabilistic reward task has been reverse-translated using touchscreen-based technology for laboratory animals, including rats (Kangas et al., 2020a), mice (Luc & Kangas, 2024), and nonhuman primates (Wooldridge et al., 2021). These techniques translated for laboratory animals have subsequently proven sensitive to early life adversity (Hisey et al., 2023; Kangas et al., 2022b), chronic stress (Gonzalez et al., 2024), and drug action (Adam et al., 2023), thus verifying construct validity. This alignment across species has positioned the probabilistic reward task to contribute to medications development for neuropsychiatric conditions, as demonstrated in recent clinical trials of kappa opioid antagonists for anhedonia (Pizzagalli et al., 2020).

Taken together, these reverse-translational approaches can accelerate preclinical discovery by expanding the availability of targeted pharmacological manipulations beyond what is feasible or possible in controlled human studies. In turn, findings from these animal models inform clinical research by appraising and refining potential treatment strategies. Preserving core task structures

originally validated in humans and modified as needed for laboratory animal species provides compelling cross-species frameworks and highlights the power of reverse-translational approaches to enrich our understanding of drug action and foster a genuine bench-to-bedside pipeline.

Concurrent Electrophysiological Recording

Another growing frontier within translational endeavors in behavioral pharmacology is the concurrent integration of advanced neural recording methods while animals perform complex operant tasks. In the context of touchscreen-based cognitive assessments, the apparatus is designed to accommodate neural probes, allowing researchers to employ techniques such as electroencephalography (EEG) and local field potential (LFP) recordings to capture real-time neural responses during task performance (Carr, 2024). EEG measures electrical activity of the brain from superficial layers of the cortex. This is collected via electrodes placed on key regions of the scalp in humans and similarly localized dura leads or skull screws in rodents. LFPs are more invasive but capture electrical activity from deeper locations of the brain, in which an electrode wire is surgically implanted into a brain tissue region of interest (Buzsáki et al., 2012). Both methods allow investigators to map how psychoactive drugs modulate electrical activity in specific brain regions or circuits during tasks measuring various aspects of cognition-related behavior.

Although there are a wide variety of highly sophisticated methods to measure neural activity in laboratory animals (e.g., single unit neural recordings, calcium imaging, voltammetry, fluorescent biosensors), the value of EEG includes the ability to conduct parallel studies in human subjects using an array of non-invasive scalp electrodes positioned on a wearable cap. For example, EEG can be used across species in reverse-translated tasks to identify translational biomarkers offered by neuro-oscillatory responses (Javitt et al., 2020), which examine the

frequency/rhythm of brainwave signals over time, and event related potentials (ERPs), which are deflections in electrical activity in response to a stimulus or response event. Both methods create another important bridge between preclinical and clinical research that can provide insight into drug mechanism and further accelerate the development of medications (Blokland et al., 2015).

Notwithstanding a rich neuroscientific literature using EEG and LFP recordings in humans and rodents, their use in pharmacological assessments of behaving subjects is, to date, more limited. However, there have been several recent studies that illustrate potential in approach for work designed to inform medications development. In one example, Kangas et al. (2021) adapted the Flanker task described above for rats to measure cognitive control under conditions that incorporated EEG and LFP recordings. Specifically, animals performed a touchscreen-based task, in which intermittently presented incongruent distractors reduced response accuracy. Continuous EEG and LFP recordings from electrodes placed in key brain regions related to the processing of visual stimuli provided high levels of correspondence with behavioral outcomes during both congruent and incongruent trial types. Specifically, robust visual evoked ERPs that diverged in amplitude and latency across electrode types, emphasized that EEG and LFP yielded complementary but not identical biomarkers of behavioral performance in response to flanked stimuli.

A follow-up cross-species comparison observed similar ERPs in both rats and humans during incongruent trial types (Robble et al., 2021). In addition, both species showed increased theta-band neural oscillations, which are thought to reflect conflict-related brain activity during responses to incongruent trials. This paralleled in rats the well-established role of theta band electrical activity in human Flanker performance (Cavanagh & Frank, 2014). Treatment with the putative cognitive-enhancer, modafinil, at the doses tested did not modify behavioral or

electrophysiological outcomes in either rats or humans, despite previous reports of its ability to enhance some aspects of cognition-related behavior (Minzenberg et al., 2008). Nevertheless, defining these spectral outcomes across species allows for a neural biomarker to supplement behavioral phenotypes in subsequent mechanistic pursuits of medications development for disorders in which deficits in cognitive control are prominent.

Within the context of reward processing-related touchscreen tasks, Cavanagh et al. (2021, 2022) demonstrated how EEG metrics can capture reinforcement-related positive deflections in ERPs in mice, mirroring known ERP components in humans (Holroyd et al., 2008; Proudfit, 2015). The magnitude of these ERPs in both species have also been shown to correlate with the degree of positive reward prediction error, in which "better than expected" or "surprise" outcomes are experienced. Importantly, from a clinical perspective, these ERPs have been observed to be blunted in patients with major depression (Bress et al., 2013). In their cross-species adaptation of a probabilistic learning task (not to be confused with the probabilistic reward task) for rodents and humans, each session comprised 60 trials divided into three blocks in which pairs of unique stimuli were presented and responses to one (rich) stimulus were reinforced at a higher probability (e.g., 80%) than responses to the other (lean) stimulus (e.g., 20%). In the subsequent blocks, the asymmetry of rich/lean reinforcement probabilities was reduced. In this paradigm, asymmetric probabilistic reinforcement produced a robust response bias towards the rich stimulus. EEG recordings during task performance reveal distinct positive deflections in ERP components and associated delta (1–5 Hz) and alpha/beta (8–20 Hz) brain activity in both species. That is, these recordings appear to serve as an objective biomarker of when humans or mice are "surprised" by the trial outcome, also known as a reward prediction error signal.

Critically, during pharmacological challenges, amphetamine potentiated ERP amplitude of these reinforcement-related signals in both humans and rats in a dose-dependent manner. In addition, delta-brain activity was also enhanced in humans but not mice following treatment with amphetamine, highlighting a notable species-specific difference. Taken together, this proof-of-concept study suggests that electrophysiological readouts, such as ERP amplitudes following reinforcement, could aid drug screening by providing a cross-species and translationally relevant biomarker that is sensitive to pharmacological action. For example, a candidate drug that enhances reward positivity in rodents might show analogous electrophysiological improvements in subsequent clinical trials with human patients with major depression or other neuropsychiatric illness in which reward processing deficits are prevalent.

Finally, using the reverse-translated probabilistic reward task to examine anhedonia described above, Iturra-Mena et al. (2023b) identified concordance across species and documented robust neurophysiological signatures of reinforcement learning in rats that are similar to those observed in humans. When humans complete this task, robust ERPs have been associated with the more richly rewarded stimulus in healthy subjects, whereas diminished positive ERP amplitudes have been observed during reward feedback in subjects with remitted major depression (Whitton et al., 2016). In rats, skull screw EEG electrodes and LFP wires were implanted in similar key brain regions relevant to reinforcement learning documented in previous human studies. Reinforcement-related ERPs during the rat probabilistic reward task resembled a negative deflection in the LFPs that was highly similar to that previously described in humans (Santesso et al., 2008). In addition, consistent with human EEG studies highlighting increased delta activity in response to reinforcement (Carlson et al., 2011), neuro-oscillatory analyses in rats highlighted an increased delta power after reward feedback.

This cross-species continuity was subsequently utilized during preclinical drug development studies of nociceptin receptor antagonists that have been shown to produce putative antidepressant-like effects in preclinical models (Gavioli et al., 2003). Interestingly, although treatment with the nociceptin antagonist J-113397 failed to produce significant modifications of behavioral performance in the probabilistic reward task, it was nevertheless able to potentiate electrophysiological signatures of reward sensitivity, including enhanced neuro-oscillatory responses to reinforcement following drug treatment (Iturra-Mena et al., 2023a). Although divergent outcomes across levels of analysis leave unclear their comparative relevance to clinical populations with depression, these behavioral and electrophysiological indices of reinforcement learning deserve further study to determine their predictive value.

More generally, findings from the studies summarized above highlight the value of supplementing behavioral measures with electrophysiological biomarkers to identify neural signatures of complex behavioral performance. They raise the possibility that rats and humans share similar neural mechanisms to regulate these behavioral processes. Such concurrent approaches are still in development but appear well positioned to provide innovative cross-species means to appraise candidate therapeutics for conditions in which cognitive control, reinforcement learning, or other complex behavior is impaired.

Conclusion

The evolution of behavioral pharmacology over the past seven decades has included remarkable innovation and continuous refinement. Early foundational assays—such as schedule-controlled responding, drug self-administration, and drug discrimination—continue to provide critical insights into the fundamental pharmacological properties of psychoactive substances. They

also laid the groundwork for understanding the complex interplay between behavior and drug action.

Building on these successes, the field has embraced preclinical models that extend far beyond the study of drugs as antecedents or consequences of operant behavior. In recent years, researchers have made significant strides in developing translational models that more accurately capture the multifaceted nature of human conditions. In pain research, for example, models that integrate both reflexive and operant measures have advanced our ability to assess not only the efficacy of analgesics but also their potential for adverse effects such as sedation and abuse liability, which may hamper the restoration of function required for satisfactory quality of life. Likewise, the advent of touchscreen-based cognitive tasks has opened new avenues for exploring a range of complex behavioral domains within a single, flexible platform. These approaches, with their capacity for multi-task batteries and close alignment with human neuropsychological assessments, have significantly enhanced the predictive and construct validity of preclinical studies. Moreover, the reverse translational approach—adapting tasks originally designed for human research to laboratory animal models—has fostered a critical bidirectional dialogue between clinical and preclinical investigators (Linton et al., 2024; Robble et al., 2021). By preserving core task structures, researchers can generate direct comparisons across species, facilitating a deeper understanding of the neurobiological underpinnings of behavioral deficits and drug action. This integrated framework not only enriches our mechanistic insights but also accelerates the discovery and optimization of candidate medications.

Looking forward, the continued evolution of behavioral pharmacology promises to further bridge the gap between the laboratory and the clinic. Advances in concurrent electrophysiological recording are already refining our ability to identify neural biomarkers and elucidate circuit-level

mechanisms underlying complex behavior. As these techniques mature and become more widely adopted, they will undoubtedly play a pivotal role in medications development and improve therapeutic outcomes. This dynamic landscape not only reaffirms the importance of behavioral pharmacology in addressing public health concerns but also sets the stage for future breakthroughs to further enhance our capacity to develop safer, more effective treatments for patients with unmet clinical needs.

References

Adam, A. S., LaMalfa, K. S., Razavi, Y., Kohut, S. J., & Kangas, B. D. (2024). A multimodal preclinical assessment of MDMA in female and male rats: Prohedonic, cognition disruptive, and prosocial effects. *Psychedelic Medicine, 2*(2), 96–108. https://doi.org/10.1089/psymed.2023.0049

Allain, F., & Samaha, A. N. (2019). Revisiting long-access versus short-access cocaine self-administration in rats: Intermittent intake promotes addiction symptoms independent of session length. *Addiction Biology, 24*(4), 641–651. https://doi.org/10.1111/adb.12629

Allen, M. I., Costa, M. B., Johnson, B. N., Gould, R. W., & Nader, M. A. (2024). Cognitive performance as a behavioral phenotype associated with cocaine self-administration in female and male socially housed monkeys. *Neuropsychopharmacology, 49*(11), 1729–1737. https://doi.org/10.1038/s41386-024-01882-7

Ator, N. A., & Griffiths, R. R. (2003). Principles of drug abuse liability assessment in laboratory animals. *Drug and Alcohol Dependence, 70*(3 Suppl), S55–S72. https://doi.org/10.1016/s0376-8716(03)00099-1

Banks, M. L., & Negus, S. S. (2017). Insights from preclinical choice models on treating drug addiction. *Trends in Pharmacological Sciences, 38*(2), 181–194. https://doi.org/10.1016/j.tips.2016.11.002

Barrett J. E. (2002). The emergence of behavioral pharmacology. *Molecular Interventions, 2*(8), 470–475. https://doi.org/10.1124/mi.2.8.470

Bergman, J., & Paronis, C. A. (2006). Measuring the reinforcing strength of abused drugs. *Molecular Interventions, 6*(5), 273–283. https://doi.org/10.1124/mi.6.5.9

Blokland, A., Prickaerts, J., van Duinen, M., & Sambeth, A. (2015). The use of EEG parameters as predictors of drug effects on cognition. *European Journal of Pharmacology, 759*, 163–168. https://doi.org/10.1016/j.ejphar.2015.03.031

Blough, D. S. (1959). Delayed matching in the pigeon. *Journal of the Experimental Analysis of Behavior*, *2*(2), 151–160. https://doi.org/10.1901/jeab.1959.2-151

Blough, D. S. (1967). Stimulus generalization as signal detection in pigeons. *Science, 158*(3803), 940–941. https://doi.org/10.1126/science.158.3803.940

Branch, M. N. (2006). How research in behavioral pharmacology informs behavioral science. *Journal of the Experimental Analysis of Behavior, 85*(3), 407–423. https://doi.org/10.1901/jeab.2006.130-04

Bress, J. N., Foti, D., Kotov, R., Klein, D. N., & Hajcak, G. (2013). Blunted neural response to rewards prospectively predicts depression in adolescent girls. *Psychophysiology*, *50*(1), 74–81. https://doi.org/10.1111/j.1469-8986.2012.01485.x

Bussey, T. J., Padain, T. L., Skillings, E. A., Winters, B. D., Morton, A. J., & Saksida, L. M. (2008). The touchscreen cognitive testing method for rodents: How to get the best out of your rat. *Learning & Memory, 15*(7), 516–523. https://doi.org/10.1101/lm.987808

Buzsáki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. *Nature Reviews Neuroscience*, *13*(6), 407–420. https://doi.org/10.1038/nrn3241

Carlson, J. M., Foti, D., Mujica-Parodi, L. R., Harmon-Jones, E., & Hajcak, G. (2011). Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: A combined ERP and fMRI study. *NeuroImage, 57*(4), 1608–1616. https://doi.org/10.1016/j.neuroimage.2011.05.037

Carr G. V. (2025). Electrophysiological recording during touchscreen-based behavioral assays in rodents: A platform for improving early-stage neuroscience drug discovery. *Journal of Neurochemistry, 169*(1), e16289. https://doi.org/10.1111/jnc.16289

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences, 18*(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Cavanagh, J. F., Gregg, D., Light, G. A., Olguin, S. L., Sharp, R. F., Bismark, A. W., Bhakta, S. G., Swerdlow, N. R., Brigman, J. L., & Young, J. W. (2021). Electrophysiological biomarkers of behavioral dimensions from cross-species paradigms. *Translational Psychiatry, 11*(1), 482. https://doi.org/10.1038/s41398-021-01562-w

Cavanagh, J. F., Olguin, S. L., Talledo, J. A., Kotz, J. E., Roberts, B. Z., Nungaray, J. A., Sprock, J., Gregg, D., Bhakta, S. G., Light, G. A., Swerdlow, N. R., Young, J. W., & Brigman, J. L. (2022). Amphetamine alters an EEG marker of reward processing in humans and mice. *Psychopharmacology, 239*(3), 923–933. https://doi.org/10.1007/s00213-022-06082-z

Christie, C., Baker, C., Cooper, C., Kennedy, P. J., Madras, B., & Bondi, P. (2017). The president's commission on combating drug addiction and the opioid crisis. https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

Corbett, A. D., Henderson, G., McKnight, A. T., & Paterson, S. J. (2006). 75 years of opioid research: The exciting but vain quest for the Holy Grail. *British Journal of Pharmacology, 147* (Suppl 1), S153–S162. https://doi.org/10.1038/sj.bjp.0706435

Crowley, M. L., Restrepo, L. F., Gamez-Jimenez, L. R., Patel, A., Braun, T., Pallares, V. L. C., Ho, N. P., Reeves, M. E., McCurdy, C. R., McMahon, L. R., & Hiranita, T. (2021). The use of hypercapnic conditions to assess opioid-induced respiratory depression in rats.

Journal of Pharmacological and Toxicological Methods, 111, 107101. https://doi.org/10.1016/j.vascn.2021.107101

Deneau, G., Yanagita, T., & Seevers, M. H. (1969). Self-administration of psychoactive substances by the monkey. *Psychopharmacologia, 16*(1), 30–48. https://doi.org/10.1007/BF00405254

Der-Avakian, A., & Markou, A. (2012). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences, 35*(1), 68–77. https://doi.org/10.1016/j.tins.2011.11.005

Desai, R. I., & Bergman, J. (2015). Effects of the nanoparticle-based vaccine, SEL-068, on nicotine discrimination in squirrel monkeys. *Neuropsychopharmacology, 40*(9), 2207–2216. https://doi.org/10.1038/npp.2015.64

Dews, P. B. (1955). Studies on behavior. I. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. *Journal of Pharmacology and Experimental Therapeutics, 113*(4), 393–401. https://doi.org10.1016/S0022-3565(25)11525-5

Dews P. B. (1987). An outsider on the inside. *Journal of the Experimental Analysis of Behavior, 48*(3), 459–462. https://doi.org/10.1901/jeab.1987.48-459

Dubner R. (1983). Pain research in animals. *Annals of the New York Academy of Sciences, 406*, 128–132. https://doi.org/10.1111/j.1749-6632.1983.tb53494.x

Dumont, J. R., Salewski, R., & Beraldo, F. (2021). Critical mass: The rise of a touchscreen technology community for rodent cognitive testing. *Genes, Brain, and Behavior, 20*(1), e12650. https://doi.org/10.1111/gbb.12650

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics, 16*(1), 143–149. https://doi.org/10.3758/BF03203267

Ferster, C. B., & Skinner, B. F. (1957). Schedules of Reinforcement. Appleton-Century-Crofts. https://doi.org/10.1037/10627-000

France, C. P., & Gerak, L. R. (1997). Discriminative stimulus effects of flumazenil in rhesus monkeys treated chronically with chlordiazepoxide. *Pharmacology, Biochemistry, and Behavior, 56*(3), 447–455. https://doi.org/10.1016/s0091-3057(96)00226-2

France, C. P., de Costa, B. R., Jacobson, A. E., Rice, K. C., & Woods, J. H. (1990). Apparent affinity of opioid antagonists in morphine-treated rhesus monkeys discriminating between saline and naltrexone. *Journal of Pharmacology and Experimental Therapeutics, 252*(2), 600–604. https://doi.org/10.1016/S0022-3565(25)19958-8

Franken, I. H., van Strien, J. W., Franzek, E. J., & van de Wetering, B. J. (2007). Error-processing deficits in patients with cocaine dependence. *Biological Psychology, 75*(1), 45–51. https://doi.org/10.1016/j.biopsycho.2006.11.003

Galbo-Thomma, L.K., Czoty, P.W. (2023). The use of touchscreen-based methods to characterize effects of psychoactive drugs on executive function in nonhuman primates. *Current Pharmacology Reports, 9*, 540–562. https://doi.org/10.1007/s40495-023-00337-9

Gavioli, E. C., Marzola, G., Guerrini, R., Bertorelli, R., Zucchini, S., De Lima, T. C., Rae, G. A., Salvadori, S., Regoli, D., & Calo, G. (2003). Blockade of nociceptin/orphanin FQ-NOP receptor signalling produces antidepressant-like effects: pharmacological and genetic evidences from the mouse forced swimming test. *European Journal of Neuroscience*, *17*(9), 1987–1990. https://doi.org/10.1046/j.1460-9568.2003.02603.x

Geller, I., Seifter, J. (1960). The effects of meprobamate, barbiturates, d-amphetamine and promazine on experimentally induced conflict in the rat. *Psychopharmacologia, 1*, 482–492. https://doi.org/10.1007/BF00429273

Gellert, V. F., & Holtzman, S. G. (1979). Discriminative stimulus effects of naltrexone in the morphine-dependent rat. *Journal of Pharmacology and Experimental Therapeutics, 211*(3), 596–605. https://doi.org/10.1016/S0022-3565(25)31880-X

Girden, E., & Culler, E. (1937). Conditioned responses in curarized striate muscle in dogs. *Journal of Comparative Psychology, 23*(2), 261–274. https://doi.org/10.1037/h0058634

Glennon, R. A., & Young, R. (2011). An introduction to drug discrimination. In R. A. Glennon & R. Young (Eds.), Drug discrimination: Applications to medicinal chemistry and drug studies (pp. 3–17). Wiley. https://doi.org/10.1002/9781118023150.ch1

Gonzalez, P. M., Jenkins, A. R., LaMalfa, K. S., & Kangas, B. D. (2024). Chronic ecologically relevant stress effects on reverse-translated touchscreen assays of reward responsivity and attentional processes in male rats: Implications for depression. *Journal of Neurochemistry, 168*(9), 2190–2200. https://doi.org/10.1111/jnc.16157

Gregory, N. S., Harris, A. L., Robinson, C. R., Dougherty, P. M., Fuchs, P. N., & Sluka, K. A. (2013). An overview of animal models of pain: Disease models and outcome measures. *Journal of Pain, 14*(11), 1255–1269. https://doi.org/10.1016/j.jpain.2013.06.008

Harlow, H. F. (1949). The formation of learning sets. *Psychological Review, 56*(1), 51–65. https://doi.org/10.1037/h0062474

Hisey, E. E., Fritsch, E. L., Newman, E. L., Ressler, K. J., Kangas, B. D., & Carlezon, W. A., Jr (2023). Early life stress in male mice blunts responsiveness in a translationally-relevant

reward task. *Neuropsychopharmacology, 48*(12), 1752–1759. https://doi.org/10.1038/s41386-023-01610-7

Hodos W. (1961). Progressive ratio as a measure of reward strength. *Science*, *134*(3483), 943–944. https://doi.org/10.1126/science.134.3483.943

Holroyd, C. B., Pakzad-Vaezi, K. L., & Krigolson, O. E. (2008). The feedback correct-related positivity: sensitivity of the event-related brain potential to unexpected positive feedback. *Psychophysiology, 45*(5), 688–697. https://doi.org/10.1111/j.1469-8986.2008.00668.x

Hvoslef-Eide, M., Nilsson, S. R., Saksida, L. M., & Bussey, T. J. (2016). Cognitive Translation Using the Rodent Touchscreen Testing Approach. *Current Topics in Behavioral Neurosciences, 28,* 423–447. https://doi.org/10.1007/7854_2015_5007

Iturra-Mena, A. M., Kangas, B. D., & Pizzagalli, D. A. (2023a). Nociceptin Receptor Antagonism Modulates Electrophysiological Markers of Reward Learning. *International Journal of Neuropsychopharmacology*, *26*(7), 496–500. https://doi.org/10.1093/ijnp/pyad031

Iturra-Mena, A. M., Kangas, B. D., Luc, O. T., Potter, D., & Pizzagalli, D. A. (2023b). Electrophysiological signatures of reward learning in the rodent touchscreen-based Probabilistic Reward Task. *Neuropsychopharmacology, 48*(4), 700–709. https://doi.org/10.1038/s41386-023-01532-4

Javitt, D. C., Siegel, S. J., Spencer, K. M., Mathalon, D. H., Hong, L. E., Martinez, A., Ehlers, C. L., Abbas, A. I., Teichert, T., Lakatos, P., & Womelsdorf, T. (2020). A roadmap for development of neuro-oscillations as translational biomarkers for treatment development in neuropsychopharmacology. *Neuropsychopharmacology, 45*(9), 1411–1422. https://doi.org/10.1038/s41386-020-0697-9

Jirkof, P., Fleischmann, T., Cesarovic, N., Rettich, A., Vogel, J., & Arras, M. (2013). Assessment of postsurgical distress and pain in laboratory mice by nest complexity scoring. *Laboratory Animals, 47*(3), 153–161. https://doi.org/10.1177/0023677213475603

Kangas B. D. (2022). Examining the effects of psychoactive drugs on complex behavioral processes in laboratory animals. *Advances in Pharmacology*, *93*, 243–274. https://doi.org/10.1016/bs.apha.2021.09.001

Kangas, B. D., & Bergman, J. (2012). A novel touch-sensitive apparatus for behavioral studies in unrestrained squirrel monkeys. *Journal of Neuroscience Methods, 209*(2), 331–336. https://doi.org/10.1016/j.jneumeth.2012.06.028

Kangas, B. D., & Bergman, J. (2014a). Operant nociception in nonhuman primates. *Pain, 155*(9), 1821–1828. https://doi.org/10.1016/j.pain.2014.06.010

Kangas, B. D., & Bergman, J. (2014b). Repeated acquisition and discrimination reversal in the squirrel monkey (Saimiri sciureus). *Animal Cognition*, *17*(2), 221–228. https://doi.org/10.1007/s10071-013-0654-7

Kangas, B. D., & Bergman, J. (2017). Touchscreen technology in the study of cognition-related behavior. *Behavioural Pharmacology, 28*(8), 623–629. https://doi.org/10.1097/FBP.0000000000000356

Kangas, B. D., & Maguire, D. R. (2016). Drug discrimination and the analysis of private events. *Behavior Analysis: Research and Practice, 16*(4), 159–168. https://doi.org/10.1037/bar0000032

Kangas, B. D., Der-Avakian, A., & Pizzagalli, D. A. (2022a). Probabilistic reinforcement learning and anhedonia. *Current Topics in Behavioral Neurosciences, 58*, 355–377. https://doi.org/10.1007/7854_2022_349

Kangas, B. D., Iturra-Mena, A. M., Robble, M. A., Luc, O. T., Potter, D., Nickels, S., Bergman, J., Carlezon, W. A., Jr, & Pizzagalli, D. A. (2021). Concurrent electrophysiological recording and cognitive testing in a rodent touchscreen environment. *Scientific Reports, 11*(1), 11665. https://doi.org/10.1038/s41598-021-91091-9

Kangas, B. D., Leonard, M. Z., Shukla, V. G., Alapafuja, S. O., Nikas, S. P., Makriyannis, A., & Bergman, J. (2016). Comparisons of Δ^9-tetrahydrocannabinol and anandamide on a battery of cognition-related behavior in nonhuman primates. *Journal of Pharmacology and Experimental Therapeutics*, *357*(1), 125–133. https://doi.org/10.1124/jpet.115.228189

Kangas, B. D., Short, A. K., Luc, O. T., Stern, H. S., Baram, T. Z., & Pizzagalli, D. A. (2022b). A cross-species assay demonstrates that reward responsiveness is enduringly impacted by adverse, unpredictable early-life experiences. *Neuropsychopharmacology, 47*(3), 767–775. https://doi.org/10.1038/s41386-021-01250-9

Kangas, B. D., Wooldridge, L. M., Luc, O. T., Bergman, J., & Pizzagalli, D. A. (2020a). Empirical validation of a touchscreen probabilistic reward task in rats. *Translational Psychiatry, 10*(1), 285. https://doi.org/10.1038/s41398-020-00969-1

Kangas, B. D., Zakarian, A. S., Vemuri, K., Alapafuja, S. O., Jiang, S., Nikas, S. P., Makriyannis, A., & Bergman, J. (2020b). Cannabinoid antagonist drug discrimination in nonhuman primates. *Journal of Pharmacology and Experimental Therapeutics, 372*(1), 119–127. https://doi.org/10.1124/jpet.119.261818

Katz, J. L., & Goldberg, S. R. (1988). Preclinical assessment of abuse liability of drugs. *Agents and Actions, 23*(1-2), 18–26. https://doi.org/10.1007/BF01967174

Kosten, T. R., & George, T. P. (2002). The neurobiology of opioid dependence: Implications for treatment. *Science & Practice Perspectives, 1*(1), 13–20. https://doi.org/10.1151/spp021113

Le Bars, D., Gozariu, M., & Cadden, S. W. (2001). Animal models of nociception. *Pharmacological Reviews, 53*(4), 597–652. https://doi.org/10.1016/S0031-6997(24)01514-X

LeSage, M. G., Shelley, D., Ross, J. T., Carroll, F. I., & Corrigall, W. A. (2009). Effects of the nicotinic receptor partial agonists varenicline and cytisine on the discriminative stimulus effects of nicotine in rats. *Pharmacology, Biochemistry, and Behavior, 91*(3), 461–467. https://doi.org/10.1016/j.pbb.2008.08.024

Levin, E. D., & Buccafusco, J. J. (Eds.). (2006). Animal Models of Cognitive Impairment. CRC Press/Taylor & Francis.

Linton, S. R., Lees, T., Iturra-Mena, A., Kangas, B. D., Nowicki, G., Lobien, R., Vitaliano, G., Bergman, J., Carlezon, W. A., Jr, & Pizzagalli, D. A. (2024). Behavioral and neurophysiological signatures of cognitive control in humans and rats. *International Journal of Neuropsychopharmacology, 27*(11), pyae050. https://doi.org/10.1093/ijnp/pyae050

Luc, O. T., & Kangas, B. D. (2024). Validation of a touchscreen probabilistic reward task for mice: A reverse-translated assay with cross-species continuity. *Cognitive, Affective & Behavioral Neuroscience, 24*(2), 281–288. https://doi.org/10.3758/s13415-023-01128-x

Luc, O. T., Pizzagalli, D. A., & Kangas, B. D. (2021). Toward a quantification of anhedonia: Unified matching law and signal detection for clinical assessment and drug development.

Perspectives on Behavior Science, 44(4), 517–540. https://doi.org/10.1007/s40614-021-00288-w

Luciana M. (2003). Practitioner review: Computerized assessment of neuropsychological function in children: Clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 44*(5), 649–663. https://doi.org/10.1111/1469-7610.00152

Mackworth, N. H. (1948). The breakdown of vigilance during prolonged visual search. Quarterly Journal of Experimental Psychology, 1, 6–21. https://doi.org/10.1080/1747021480841673

Mansbach, R. S., Feltner, D. E., Gold, L. H., & Schnoll, S. H. (2003). Incorporating the assessment of abuse liability into the drug discovery and development process. *Drug and Alcohol Dependence, 70*(3 Suppl), S73–S85. https://doi.org/10.1016/s0376-8716(03)00100-5

Mao J. (2012). Current challenges in translational pain research. *Trends in Pharmacological Sciences, 33*(11), 568–573. https://doi.org/10.1016/j.tips.2012.08.001

Matthies, B. K., & Franklin, K. B. J. (1992). Formalin pain is expressed in decerebrate rats but not attenuated by morphine. *Pain, 51*(2), 199–206. https://doi.org/10.1016/0304-3959(92)90261-9

McGuire, P. S., & Seiden, L. S. (1980). Differential effects of imipramine in rats as a function of DRL schedule value. *Pharmacology, Biochemistry, and Behavior, 13*(5), 691–694. https://doi.org/10.1016/0091-3057(80)90013-1

McKearney, J. W. (1981). Rate dependency: Scope and limitations in the explanation and analysis of the behavioral effects of drugs. *Advances in Behavioral Pharmacology, 3*, 91–109. https://doi.org/10.1016/B978-0-12-004703-1.50013-9.

McMahon L. R. (2015). The rise (and fall?) of drug discrimination research. *Drug and Alcohol Dependence, 151*, 284–288. https://doi.org/10.1016/j.drugalcdep.2015.04.001

Meier, P. M., & Reinagel, P. (2013). Rats and humans differ in processing collinear visual features. *Frontiers in Neural Circuits, 7*, 197. https://doi.org/10.3389/fncir.2013.00197

Minzenberg, M. J., & Carter, C. S. (2008). Modafinil: A review of neurochemical actions and effects on cognition. *Neuropsychopharmacology*, *33*(7), 1477–1502. https://doi.org/10.1038/sj.npp.1301534

Mogil J. S. (2009). Animal models of pain: Progress and challenges. *Nature Reviews Neuroscience, 10*(4), 283–294. https://doi.org/10.1038/nrn2606

Mullane, J. C., Corkum, P. V., Klein, R. M., & McLaughlin, E. (2009). Interference control in children with and without ADHD: A systematic review of Flanker and Simon task performance. *Child Neuropsychology, 15*(4), 321–342. https://doi.org/10.1080/09297040802348028

Nagahara, A. H., Bernot, T., & Tuszynski, M. H. (2010). Age-related cognitive deficits in rhesus monkeys mirror human deficits on an automated test battery. *Neurobiology of Aging, 31*(6), 1020–1031. https://doi.org/10.1016/j.neurobiolaging.2008.07.007

Negus S. S. (2018). Addressing the Opioid Crisis: The Importance of Choosing Translational Endpoints in Analgesic Drug Discovery. *Trends in Pharmacological Sciences, 39*(4), 327–330. https://doi.org/10.1016/j.tips.2018.02.002

Negus, S. S., Neddenriep, B., Altarifi, A. A., Carroll, F. I., Leitl, M. D., & Miller, L. L. (2015). Effects of ketoprofen, morphine, and kappa opioids on pain-related depression of nesting in mice. *Pain, 156*(6), 1153–1160. https://doi.org/10.1097/j.pain.0000000000000171

Neubert, J. K., Widmer, C. G., Malphurs, W., Rossi, H. L., Vierck, C. J., Jr, & Caudle, R. M. (2005). Use of a novel thermal operant behavioral assay for characterization of orofacial pain sensitivity. *Pain, 116*(3), 386–395. https://doi.org/10.1016/j.pain.2005.05.011

Nguyen, J. D., Aarde, S. M., Vandewater, S. A., Grant, Y., Stouffer, D. G., Parsons, L. H., Cole, M., & Taffe, M. A. (2016). Inhaled delivery of Δ(9)-tetrahydrocannabinol (THC) to rats by e-cigarette vapor technology. *Neuropharmacology, 109*, 112–120. https://doi.org/10.1016/j.neuropharm.2016.05.021

O'Connor, E. C., Chapman, K., Butler, P., & Mead, A. N. (2011). The predictive validity of the rat self-administration model for abuse liability. *Neuroscience and Biobehavioral Reviews, 35*(3), 912–938. https://doi.org/10.1016/j.neubiorev.2010.10.012

Overton D. A. (1964). State-dependent or "dissociated" learning produced with pentobarbital. *Journal of Comparative and Physiological Psychology, 57*, 3–12. https://doi.org/10.1037/h0048023

Overton D. A. (1982). Multiple drug training as a method for increasing the specificity of the drug discrimination procedure. *Journal of Pharmacology and Experimental Therapeutics, 221*(1), 166–172. https://doi.org/10.1016/S0022-3565(25)33033-8

Palmer, D., Dumont, J. R., Dexter, T. D., Prado, M. A. M., Finger, E., Bussey, T. J., & Saksida, L. M. (2021). Touchscreen cognitive testing: Cross-species translation and co-clinical trials in neurodegenerative and neuropsychiatric disease. *Neurobiology of Learning and Memory, 182*, 107443. https://doi.org/10.1016/j.nlm.2021.107443

Panlilio, L. V., & Goldberg, S. R. (2007). Self-administration of drugs in animals and humans as a model and an investigative tool. *Addiction, 102*(12), 1863–1870. https://doi.org/10.1111/j.1360-0443.2007.02011.x

Patino, L. R., Adler, C. M., Mills, N. P., Strakowski, S. M., Fleck, D. E., Welge, J. A., & DelBello, M. P. (2013). Conflict monitoring and adaptation in individuals at familial risk for developing bipolar disorder. *Bipolar Disorders, 15*(3), 264–271. https://doi.org/10.1111/bdi.12059

Pitcher, T., Sousa-Valente, J., & Malcangio, M. (2016). The monoiodoacetate model of osteoarthritis pain in the mouse. *Journal of Visualized Experiments : JoVE*, (111), 53746. https://doi.org/10.3791/53746

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biological Psychiatry, 57*(4), 319–327. https://doi.org/10.1016/j.biopsych.2004.11.026

Pizzagalli, D. A., Peccoralo, L. A., Davidson, R. J., & Cohen, J. D. (2006). Resting anterior cingulate activity and abnormal responses to errors in subjects with elevated depressive symptoms: A 128-channel EEG study. *Human Brain Mapping, 27*(3), 185–201. https://doi.org/10.1002/hbm.20172

Pizzagalli, D. A., Smoski, M., Ang, Y. S., Whitton, A. E., Sanacora, G., Mathew, S. J., Nurnberger, J., Jr, Lisanby, S. H., Iosifescu, D. V., Murrough, J. W., Yang, H., Weiner, R. D., Calabrese, J. R., Goodman, W., Potter, W. Z., & Krystal, A. D. (2020). Selective kappa-opioid antagonism ameliorates anhedonic behavior: Evidence from the Fast-fail Trial in Mood and Anxiety Spectrum Disorders (FAST-MAS).

Neuropsychopharmacology, 45(10), 1656–1663. https://doi.org/10.1038/s41386-020-0738-4

Proudfit G. H. (2015). The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology, 52*(4), 449–459. https://doi.org/10.1111/psyp.12370

Rainville, P., Feine, J. S., Bushnell, M. C., & Duncan, G. H. (1992). A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. *Somatosensory & Motor Research, 9*(4), 265–277. https://doi.org/10.3109/08990229209144776

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., McInnes, L., & Rabbitt, P. (1994). Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. *Dementia, 5*(5), 266–281. https://doi.org/10.1159/000106735

Robble, M. A., Schroder, H. S., Kangas, B. D., Nickels, S., Breiger, M., Iturra-Mena, A. M., Perlo, S., Cardenas, E., Der-Avakian, A., Barnes, S. A., Leutgeb, S., Risbrough, V. B., Vitaliano, G., Bergman, J., Carlezon, W. A., Jr, & Pizzagalli, D. A. (2021). Concordant neurophysiological signatures of cognitive control in humans and rats. *Neuropsychopharmacology, 46*(7), 1252–1262. https://doi.org/10.1038/s41386-021-00998-4

Rock, E. M., & Parker, L. A. (2016). Cannabinoids as potential treatment for chemotherapy-induced nausea and vomiting. *Frontiers in Pharmacology*, *7*, 221. https://doi.org/10.3389/fphar.2016.00221

Rodríguez-Palma, E. J., Ramos-Rodríguez, I. I., Huerta de la Cruz, S., Granados-Soto, V., & Sancho, M. (2024). Spinal nerve ligation: An experimental model to study neuropathic

pain in rats and mice. *Methods in Cell Biology, 188*, 73–88. https://doi.org/10.1016/bs.mcb.2024.03.006

Sahakian, B. J., & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: Discussion paper. *Journal of the Royal Society of Medicine, 85*(7), 399–402.

Samson, H. H., & Czachowski, C. L. (2003). Behavioral measures of alcohol self-administration and intake control: Rodent models. *International Review of Neurobiology, 54*, 107–143. https://doi.org/10.1016/s0074-7742(03)54004-1

Sanger, D. J., & Blackman, D. E. (1976). Rate-dependent effects of drugs: A review of the literature. *Pharmacology, Biochemistry, and Behavior, 4*(1), 73–83. https://doi.org/10.1016/0091-3057(76)90178-7

Santesso, D. L., Dillon, D. G., Birk, J. L., Holmes, A. J., Goetz, E., Bogdan, R., & Pizzagalli, D. A. (2008). Individual differences in reinforcement learning: Behavioral, electrophysiological, and neuroimaging correlates. *NeuroImage, 42*(2), 807–816. https://doi.org/10.1016/j.neuroimage.2008.05.032

Schindler, C. W., Panlilio, L. V., & Goldberg, S. R. (2002). Second-order schedules of drug self-administration in animals. *Psychopharmacology, 163*(3-4), 327–344. https://doi.org/10.1007/s00213-002-1157-4

Schuster, C. R., Dockens, W. S., & Woods, J. H. (1966). Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia, 9*(2), 170–182. https://doi.org/10.1007/BF00404721

Schuster, C. R., Fischman, M. W., & Johanson, C. E. (1981). Internal stimulus control and subjective effects of drugs. *NIDA Research Monograph, 37*, 116–129.

Shannon, H. E., & Holtzman, S. G. (1976). Evaluation of the discriminative effects of morphine in the rat. *Journal of Pharmacology and Experimental Therapeutics, 198*(1), 54–65.

Spillane, J., & McAllister, W. B. (2003). Keeping the lid on: A century of drug regulation and control. *Drug and Alcohol Dependence, 70*(3 Suppl), S5–S12. https://doi.org/10.1016/s0376-8716(03)00096-6

Spinelli, S., Pennanen, L., Dettling, A. C., Feldon, J., Higgins, G. A., & Pryce, C. R. (2004). Performance of the marmoset monkey on computerized tasks of attention and working memory. *Brain research. Cognitive Brain Research, 19*(2), 123–137. https://doi.org/10.1016/j.cogbrainres.2003.11.007

Spragg, S. D. S. (1940). Morphine addiction in chimpanzees. *Comparative Psychology Monographs, 15*, 7, 132.

Thompson, T., & Schuster, T. R. (1964). Morphine self-administration, food-reinforced, and avoidance behaviors in rhesus monkeys. *Psychopharmacologia, 5*, 87–94. https://doi.org/10.1007/BF00413045

United States Food and Drug Administration (FDA) (2017). Assessment of abuse potential of drugs: Guidance for industry. https://www.fda.gov/media/116739/download.

Weed, M. R., Taffe, M. A., Polis, I., Roberts, A. C., Robbins, T. W., Koob, G. F., Bloom, F. E., & Gold, L. H. (1999). Performance norms for a rhesus monkey neuropsychological testing battery: Acquisition and long-term performance. *Brain Research: Cognitive Brain Research, 8*(3), 185–201. https://doi.org/10.1016/s0926-6410(99)00020-8

Weeks J. R. (1962). Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. *Science, 138*(3537), 143–144. https://doi.org/10.1126/science.138.3537.143

Wesnes, K. A., Annas, P., Edgar, C. J., Deeprose, C., Karlsten, R., Philipp, A., Kalliomäki, J., & Segerdahl, M. (2010). Nabilone produces marked impairments to cognitive function and changes in subjective state in healthy volunteers. *Journal of Psychopharmacology*, *24*(11), 1659–1669. https://doi.org/10.1177/0269881109105900

Whitton, A. E., Kakani, P., Foti, D., Van't Veer, A., Haile, A., Crowley, D. J., & Pizzagalli, D. A. (2016). Blunted neural responses to reward in remitted major depression: A high-density event-related potential study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1*(1), 87–95. https://doi.org/10.1016/j.bpsc.2015.09.007

Withey, S. L., Maguire, D. R., & Kangas, B. D. (2020). Developing improved translational models of pain: A role for the behavioral scientist. *Perspectives on Behavior Science, 43*(1), 39–55. https://doi.org/10.1007/s40614-019-00239-6

Withey, S. L., Paronis, C. A., & Bergman, J. (2018). Concurrent assessment of the antinociceptive and behaviorally disruptive effects of opioids in squirrel monkeys. *Journal of Pain, 19*(7), 728–740. https://doi.org/10.1016/j.jpain.2018.02.003

Woods, J. H., Young, A. M., & Herling, S. (1982). Classification of narcotics on the basis of their reinforcing, discriminative, and antagonist effects in rhesus monkeys. *Federation Proceedings, 41*(2), 221–227.

Wooldridge, L. M., Bergman, J., Pizzagalli, D. A., & Kangas, B. D. (2021). Translational assessments of reward responsiveness in the marmoset. *International Journal of Neuropsychopharmacology*, *24*(5), 409–418. https://doi.org/10.1093/ijnp/pyaa090

Wooldridge, L. M., Ji, L., Liu, Y., Nikas, S. P., Makriyannis, A., Bergman, J., & Kangas, B. D. (2020). Antiemetic effects of cannabinoid agonists in nonhuman primates. *Journal of*

Pharmacology and Experimental Therapeutics, *374*(3), 462–468. https://doi.org/10.1124/jpet.120.265710

Wylie, S. A., van den Wildenberg, W. P., Ridderinkhof, K. R., Bashore, T. R., Powell, V. D., Manning, C. A., & Wooten, G. F. (2009). The effect of speed-accuracy strategy on response interference control in Parkinson's disease. *Neuropsychologia, 47*(8-9), 1844–1853. https://doi.org/10.1016/j.neuropsychologia.2009.02.025

Zinchenko, A., Al-Amin, M. M., Alam, M. M., Mahmud, W., Kabir, N., Reza, H. M., & Burne, T. H. J. (2017). Content specificity of attentional bias to threat in post-traumatic stress disorder. *Journal of Anxiety Disorders, 50*, 33–39. https://doi.org/10.1016/j.janxdis.2017.05.006