Examining the effects of psychoactive drugs on complex behavioral processes in laboratory animals

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Abstract

Behavioral pharmacology has been aided significantly by the development of innovative cognitive tasks designed to examine complex behavioral processes in laboratory animals. Performance outcomes under these conditions have provided key metrics of drug action which serve to supplement traditional in vivo assays of physiologic and behavioral effects of psychoactive drugs. This chapter provides a primer of cognitive tasks designed to assay different aspects of complex behavior, including learning, cognitive flexibility, memory, attention, motivation, and impulsivity. Both capstone studies and recent publications are highlighted throughout to illustrate task value for two distinct but often interconnected translational strategies. First, task performance in laboratory animals can be utilized to elucidate how drugs of abuse affect complex behavioral processes. Here, the expectation is that adverse effects on such processes...
will have predictive relevance to consequences that will be experienced by humans. Second, these same task outcomes can be used to evaluate candidate therapeutics. In this case, the extent to which drug doses with medicinal value perturb task performance can contribute critical information for a more complete safety profile appraisal and advance the process of medications development. Methodological and theoretical considerations are discussed and include an emphasis on determining selectivity in drug action on complex behavioral processes.

1. Introduction

Psychoactive drugs can have profound effects on complex behavioral processes. The intersection between behavioral science and pharmacology offers an approach to better understand these interactions and, like many endeavors in biomedical science, can be aided in significant ways by translational research in laboratory animals. Indeed, the last 65 years of research in behavioral pharmacology using rodents, birds, and nonhuman primates have produced substantial increases in our understanding of drug effects on behavioral processes. During the last few decades, advances in the development and empirical validation of cognitive tasks for laboratory animals have served as important complements to efforts elucidating drug action using other behavioral methodologies, including schedule-controlled responding, drug discrimination, and self-administration.

The reasons for studying the effects of psychoactive drugs in cognitive tasks can be divided into two general categories. The first involves deriving detailed characterizations of the effects drugs of abuse have on complex behavioral processes. Here, the expectation is that either brief or long-term perturbations in task performance following either acute or chronic drug treatment will be predictive of consequences experienced by humans. That is, understanding how commonly used and abused drugs adversely affect different aspects of complex behavioral processes allows for an enhanced appraisal of inherent risks which can be levied against perceived recreational benefits.

A second reason for studying the effects of psychoactive drugs on cognitive task performance in laboratory animals is to evaluate candidate therapeutics on complex behavioral processes. In this case, determining the effects of a novel pharmacotherapeutic on task performance at doses known to have medicinal value can contribute to a preclinical appraisal of the drug’s safety. Indeed, establishing a therapeutic index that quantifies the distance between doses that produce desirable treatment outcomes and those that adversely
affect task performance can complement traditional toxicological measures (Weiss & Laties, 1975) and indices of abuse liability (Ator & Griffiths, 2003) for appraising a candidate medication’s clinical viability and side-effect profile. In some cases, an established pharmacotherapeutic may have adverse effects on cognition that are targeted for reduction or elimination in a novel candidate medication. Thus, a preclinical approach that defines the existing therapeutic as a standard to improve upon, via retention of medicinal effects with fewer unwanted behaviorally disruptive effects, can serve to advance drug development.

Importantly, although the two approaches described above can be conducted independently, it is increasingly common for these pursuits to progress in a highly interconnected manner. For example, many endeavors in the development of psychoactive therapeutics focus on improving the safety profile of existing medications. Often, these existing medications, though efficacious for their intended purposes, are also drugs of abuse in certain populations. Indeed, abuse liability is a common undesirable feature of several categories of commonly prescribed pharmacotherapies, including opioid analgesics for pain management (Wightman, Perrone, Portelli, & Nelson, 2012), psychomotor stimulants for attention deficit disorders (Romach, Schoedel, & Sellers, 2014), and benzodiazepines for anxiety (Ator, 2005). Having the existing medication serve as the standard to be improved upon allows for systematic comparisons of candidate therapeutics designed to have lower abuse liability while simultaneously evaluating potential for accompanying side-effects on complex behavioral processes. This strategy can provide a more complete preclinical safety profile of both existing and candidate medications and, at the same time, reveal potentially hazardous consequences for those who might consume it illicitly.

2. Cognitive tasks in pharmacology

This section is designed to serve as a primer of commonly used cognitive tasks in laboratory animals for the pursuits in behavioral pharmacology and medications development defined above. It is important to note that this is not intended to serve as an exhaustive list. In fact, novel methods are continually being developed to examine behavioral phenotypes that emerge from clinical observations and laboratory discoveries. Rather, the diverse tasks highlighted in this chapter are examples of those associated with long-standing contributions to an enhanced understanding of drug action on complex behavioral processes. Finally, it is important to note that every
task discussed below can be understood from a neuropharmacological perspective that seeks to explicate their neurobiological and pharmacological mechanisms of action; however, the scope of this chapter expressly prioritizes the behavioral level of analysis. Nevertheless, many of the references cited below were selected to guide the interested reader to the relevant neural and receptor pharmacology literature as well.

2.1 Learning

The extent to which a drug perturbs learning can provide a foundational assessment of its actions on complex behavioral processes. In particular, discrimination learning has provided a vital approach to the study of both abused drugs and candidate medications. Studying the rate at which a subject acquires a new discrimination allows for measurement of the magnitude of a drug’s adverse consequences and the extent to which tolerance develops to those effects. Discriminative behavior can also be used as a means to determine a subject’s sensitivity to the reinforcement contingencies that maintain such performance and how a drug might modify those complex processes.

2.1.1 Repeated acquisition

The repeated acquisition task is an assay commonly used to examine fundamental aspects of discrimination learning and how it develops over time. In its typical arrangement, a subject is presented with two concurrently-available stimuli: one arbitrarily designated as S+ (responses to it result in reinforcement) and the other as S− (responses to it result in a timeout period). Following sufficient experience with the contingencies, subjects eventually acquire the discrimination, indicated by exclusive responding to the S+ stimulus. Following mastery of a given discrimination, the subject is exposed to a novel S+/S− pair until mastery is again observed. This is repeated with numerous S+/S− stimulus pairs across sessions to allow for measurement of acquisition rate across successive discriminations. Although it had been known for some time that laboratory animals can acquire multiple distinct discriminations, seminal work by Harlow (1949) using this paradigm in monkeys illustrated a profound effect and fundamental principle of learning: the rate at which a subject acquires such discriminations increases systematically as a function of the number of previously mastered discriminations until very few trials are required to learn new discriminations. He called this phenomenon a learning set. The importance of this finding lies not simply in the characterization of the subject’s ever-expanding discriminative repertoire but, for the present purposes, a method to examine acute drug
treatment on the ability to learn new things and how chronic drug treatment might impact the ability to develop a learning set (i.e., learn-to-learn). Although early capstone studies manually presented three-dimensional S+ / S− objects to subjects (Warren, 1965), subsequent studies in behavioral pharmacology used automated procedures in operant conditioning chambers to examine drug effects on novel discrimination learning by repeatedly training unique chained response sequences across multiple operandas (Thompson, 1973). For example, a subject responding in a chamber with two levers might need to press the left, then right, then right again, then left lever to obtain reward. These 3–5 step sequences allowed for some of the first systematic studies characterizing the deleterious effects of Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and other cannabinoid agonists in rats and monkeys (Branch, Dearing, & Lee, 1980; Thompson & Winsauer, 1985; Winsauer, Lambert, & Moerschbaecher, 1999) and subsequent tolerance (Delatte, Winsauer, & Moerschbaecher, 2002), as well as adverse stimulant and opioid effects (Evans & Wenger, 1992; Moerschbaecher, Thompson, & Winsauer, 1983; Winsauer, Silvester, Moerschbaecher, & France, 2000). More recently, advances in modern touch-sensitive technology for rodents and nonhuman primates (Bussey et al., 2008; Dumont, Salewski, & Beraldo, 2021; Kangas & Bergman, 2012, 2017) have provided an ability to train a near-infinite number of distinct visual discriminations using unique photographic stimuli (Kangas & Bergman, 2014) to examine the effects of psychoactive drugs on acquisition rates to master novel discriminations and, as well, the development of learning-to-learn repertoires. In addition to systematic replication of Δ⁹-THC’s adverse effects on discrimination learning (Withey et al., 2021), repeated acquisition studies have detailed comparisons of Δ⁹-THC and ligands designed to elevate levels of endogenous cannabinoids to examine the prospect that endocannabinoids may have similar medicinal value with fewer unwanted side-effects than Δ⁹-THC (Di Marzo, 2018). This advantage was indeed documented in learning (Kangas et al., 2016) and antiemesis (Wooldridge et al., 2020) endpoints, thus representing an instance of the important interplay between studying drugs of abuse and therapeutic potential discussed above. In addition to studies of experimenter-administered drugs, touchscreen-based repeated acquisition tasks have also been used to characterize the effects of self-administered drugs, such as methamphetamine (Kangas & Bergman, 2016) and cocaine (Kangas, Doyle, Kohut, Bergman, & Kaufman, 2019). These studies revealed that, although significant adverse effects on the rate of acquisition were associated with high daily drug intake, tolerance to the disruptive effects on learning was reliably produced following
remedial training, even during chronic conditions. Interestingly, matched studies of other self-administered drugs of abuse, for example, the prescription opioid oxycodone (Kibaly et al., 2021), have documented no deleterious effects on the development of this behavioral repertoire, even during conditions of high daily intake (Withey, Doyle, Porter, Bergman, & Kangas, 2020), providing evidence that the abuse liability of a drug does not necessarily predict its adverse effects on discrimination learning.

2.1.2 Probabilistic reward task

The probabilistic reward task is designed to examine a subject’s sensitivity to reward. It also utilizes discrimination methodology; however, in this paradigm, rather than examining the development of discrimination learning, the same two stimuli are presented across numerous trials with asymmetric probabilistic contingencies that reward correct responses in the presence of one stimulus (rich) more often than correct responses in the presence of the other stimulus (lean). This provides a quantitative means to identify reward learning deficits that are prominent in anhedonic populations and for which no approved medications exist. For example, in the human variant of the probabilistic reward task (Pizzagalli, Jahn, & O’Shea, 2005), subjects are instructed to distinguish between two lines that vary slightly in length. Unbeknownst to the subjects, 3:1 asymmetrical probabilistic contingencies are arranged such that 60% of correct responses to one of the stimuli are rewarded (e.g., long line: rich stimulus) and 20% of correct responses to the other are rewarded (e.g., short line: lean stimulus). As predicted by signal detection theory (Luc, Pizzagalli, & Kangas, 2021; McCarthy & Davison, 1979), healthy subjects reliably exhibit a response bias toward the more richly rewarded stimulus. However, subjects with anhedonia display a blunted response bias that has been repeatedly documented to correlate with current and future anhedonia across diverse clinical populations (Vrieze et al., 2013). Anhedonia, or the loss of pleasure or lack of reactivity to previously rewarding stimuli, is most closely associated with major depressive disorders (Whitton, Treadway, & Pizzagalli, 2015), but is also prominent in other neuropsychiatric conditions, including bipolar disorder (Hasler, Drevets, Gould, Gottesman, & Manji, 2006), schizophrenia (Horan, Krin, & Blanchard, 2006), post-traumatic stress disorder (Nawijn et al., 2015), and substance use disorder (Markou, Kosten, & Koob, 1998). Given the transdiagnostic prevalence of anhedonic phenotypes across neuropsychiatric disorders, the probabilistic reward task has been reverse-translated for use in rodents and non-human primates to help bridge the preclinical gap between therapeutic
discovery and treatment. For example, in an auditory-based variant, rats were trained to discriminate between two tone durations that, following acquisition, were programmed with a 3:1 rich:lean probabilistic contingency (Der-Avakian, D’Souza, Pizzagalli, & Markou, 2013). Expected response biases toward the more richly rewarded stimulus were observed as was pharmacological blunting of response bias following administration of low doses of the direct dopamine D₂-family agonist pramipexole as seen previously in humans (Pizzagalli et al., 2008). In addition, chronic social defeat stress blunted response biases relative to non-stressed controls (Der-Avakian et al., 2017) and, in turn, revealed a role of dopaminergic and glucocorticoid systems in aspects of reward responsiveness (Lamontagne, Melendez, & Olmstead, 2018). To align formal similarity with the human task, touchscreen-based variants also have been developed using visual line-length discriminations under probabilistic contingencies designed for rats (Kangas, Wooldridge, Luc, Bergman, & Pizzagalli, 2020) and marmosets (Wooldridge, Bergman, Pizzagalli, & Kangas, 2021). Expected response biases were observed in both species and subsequent studies confirmed pharmacological sensitivity by showing that drugs known to enhance hedonic tone, such as amphetamine (McIntyre et al., 2017), scopolamine (Jaffe, Novakovic, & Peselow, 2013), and ketamine (Coyle & Laws, 2015), dose-dependently enhanced reward responsiveness in these reverse-translated animal tasks. Coordinated pursuits of this sort leverage human and laboratory animal behavior under discrimination learning tasks as quantitative metrics to advance medications development for disorders in which anhedonic phenotypes are prominent.

2.2 Cognitive flexibility

Although the development of discrimination learning repertoires can be viewed as fundamental adaptive behavior, so too is the ability to modify response allocation in the face of changing contingencies. The capacity to efficiently inhibit a previously reinforced response in a shifting environment has obvious survival value and, as such, the extent to which a drug perturbs these complex behavioral processes has been a ripe source of investigation in behavioral pharmacology and medications development.

2.2.1 Discrimination reversal

The discrimination reversal task is commonly used to probe cognitive flexibility, that is, a subject’s ability to inhibit a response that was previously associated with reward delivery and respond effectively in accord with the new
contingencies. The first phase of the discrimination reversal task often mirrors that of the repeated acquisition task in which a novel S+/S− stimulus discrimination is mastered. At some point following discrimination mastery, in an otherwise unsignaled manner, responses to the stimulus that was previously S+ produces the consequences associated with the stimulus that was previously S−, and vice versa. Because this reversal in contingencies is not signaled to the subject, responses to the stimulus that was previously S+ (now S−) persist for a period of time. Following sufficient exposure to these updated conditions, the subject will inhibit this response and instead respond with increased probability to the stimulus that was previously S− (now S+). The rate at which this shift in response allocation occurs serves as a primary dependent variable related to the construct of cognitive flexibility/response inhibition and, like acquisition rate of the initial discrimination, is a highly useful behavioral endpoint to examine the effects of psychoactive drugs, especially those with high abuse liability (Izquierdo & Jentsch, 2012).

One prominent example of its use in behavioral pharmacology is in studies of psychomotor stimulants. Compulsive phenotypes defined, in part, by deficits in inhibitory control have been long associated with substance use disorders involving this drug class (London, Kohno, Morales, & Ballard, 2015). Studies examining nonhuman primate performance during a discrimination reversal task have discovered, for example, that chronic methamphetamine-induced performance deficits were significantly more pronounced during discrimination reversal, relative to initial acquisition, but also included individual differences that revealed a correlation between the magnitude of impaired cognitive flexibility and changes in dopaminergic transmission, specifically via reduced dopamine D2-like receptors and dopamine transporter availability (Groman et al., 2012). Assessments of individual differences in reversal learning and inhibitory control also uncovered a relationship between the magnitude of task deficits and structural alterations of increased gray matter density in the putamen (Groman, Morales, Lee, London, & Jentsch, 2013), in line with previous neuroimaging observations in humans (Chang et al., 2005). Increases in gray matter density, among other structural changes, were also recently shown to correlate with deficits in reversal learning following chronic self-administered cocaine, even after extended periods of abstinence (Jedema et al., 2021). These studies and others demonstrate the value of examining reversal learning and response inhibition metrics that comprise the construct of cognitive flexibility and, as well, how interrogating individual differences in task performance can reveal mechanistic order when determining behavior, drug, and brain interactions.
2.2.2 Probabilistic reversal learning

The probabilistic reversal learning task shares several features with the discrimination reversal task described above to assay cognitive flexibility but with asymmetric probabilistic contingencies programmed. Specifically, subjects are presented with a concurrent choice between two options: responding on one results in reward more often (e.g., 80% of the time), whereas responding on the other option results in reward less often (e.g., 20% of the time). After the subject is exclusively responding on the rich alternative for some predefined number of trials, the probabilities programmed on each response alternative switch in an otherwise unsignaled manner. This task is often comprised of numerous trials allowing for multiple reversals in a daily session and the number of completed reversals serves as a primary dependent measure. Like the discrimination reversal task, the shift in response allocation in the face of changing contingencies is thought to assay cognitive flexibility and, in turn, can serve as a useful construct to examine underlying neural mechanism and pharmacological modulation. In addition, as with several of the tasks highlighted in this chapter, variants designed for human subjects that are commonly used for similar ends permit coordinated studies of cross-species continuity (Fellows & Farah, 2003; Lawrence, Sahakian, Rogers, Hodge, & Robbins, 1999). Moreover, the use of probabilistic schedules of reinforcement lend themselves well to innovative computational analyses of expected and unexpected reinforcement/punishment outcomes in laboratory animals that are similar to those used in human studies (Costa, Tran, Turchi, & Averbeck, 2015; Kanen, Ersche, Fineberg, Robbins, & Cardinal, 2019). The probabilistic reversal learning task has revealed deficits in cognitive flexibility during nicotine withdrawal (Jackson, Silk, Buhidma, & Shoaib, 2017) and following chronic administration of abused drugs such as methamphetamine (Groman, Rich, Smith, Lee, & Taylor, 2018) and cocaine (Groman et al., 2020) but not alcohol (Aguirre et al., 2020). It has also been used to provide preclinical indications of performance enhancement, for example, following oxytocin treatment (Roberts et al., 2019). Recent work also has employed this task with aims to develop improved medications for mood disorders, given the fact that deficits in reversal learning have been associated with depression (Mukherjee, Filipowicz, Vo, Satterthwaite, & Kable, 2020). To date, probabilistic reversal learning studies in rats have yielded encouraging, though mixed, findings. For example, during systematic studies examining serotonergic mechanisms in sensitivity to reward and negative feedback, Bari et al. (2010) documented the ability of acute and sub-chronic treatment with a high but not low dose of citalopram to enhance reversal learning. Studies of other antidepressants have
documented that agomelatine and mirtazapine, but not escitalopram, clomipramine, and venlafaxine, improved certain aspects of reversal learning (Drozd, Rychlik, Fijalkowska, & Rygula, 2019), whereas Wilkinson, Grogan, Mellor, and Robinson (2020) also observed enhancement effects with citalopram, but not reboxetine, venlafaxine, or the fast-acting antidepressants ketamine and scopolamine (however, see Rychlik, Bollen, & Rygula, 2017, for positive ketamine findings). Rigorous testing across numerous drugs designed for the same indication serves as an important example of how to use performance outcomes under the same task to provide preclinical ranking of candidate therapeutics.

2.3 Memory

A preponderance of animal research on the behavioral pharmacology of memorial processes involves examining the effects of psychoactive drugs on delayed stimulus control. This is typically arranged by training a conditional discrimination between a stimulus (e.g., visual, auditory, or spatial cue) and a response. After the conditional discrimination has been mastered, a delay is introduced between stimulus presentation and the opportunity to respond. This procedural variable is called a retention interval and its duration is negatively correlated with performance accuracy. That is, as the retention interval increases, stimulus control decreases. Evaluation of a variety of retention intervals across trials allows for characterization of a forgetting function, usually described by a negative exponential curve which has been repeatedly documented to be sensitive to, and modified by, drug treatment.

2.3.1 Delayed matching-to-sample

The delayed matching-to-sample task is used to examine short-term recognition memory (Blough, 1959; Kangas, Berry, & Branch, 2011; White, 1985). In its most common iteration, a subject is presented with one of two sample stimuli (e.g., a red or green light centered in between a left and right response lever). After completion of an observing response in the presence of that stimulus, it is extinguished for a period of time, followed by simultaneous illumination of two comparison stimuli (a red and green light, one presented above the left and the other presented above the right lever). A correct response is defined by responding on the lever associated with the comparison stimulus that matched the physical characteristics of the previously presented sample stimulus and is reinforced, whereas selection of the non-matching stimulus will terminate the trial without reward. A range of species-relevant retention intervals are examined across trials in a mixed
manner to derive a forgetting function. Alternatively, procedural variants have been developed in which the retention interval increases following correct matches and decreases following incorrect matches and these titration contingences allow for precise determinations of memorial capacities under the conditions arranged (Cumming & Berryman, 1965; Kangas, Vaidya, & Branch, 2010). In another task variant, the *delayed matching-to-position task* is designed to assay *short-term spatial memory* (Dunnett, 1985). Instead of probing the ability to recognize a previously presented stimulus following a retention interval, a stimulus is presented in a location within the experimental chamber, for example, a light presented above one of two levers. After an observing response is made on the illuminated lever, another response is required on a different side of the chamber and, thereafter, the levers are protracted after the retention interval elapses. A response to the previously illuminated lever will be reinforced, whereas responses to other levers will terminate the trial without reward. A long-standing research domain using these tasks has detailed the adverse effects on short-term memory of diverse drugs of abuse, including alcohol (Mello, 1971), cannabinoids (Kangas et al., 2016), psychomotor stimulants (Branch & Dearing, 1982; Harper, Wisnewski, Hunt, & Schenk, 2005; Jedema et al., 2021; LeSage, Clark, & Poling, 1993) and, in the latter drug class, how pretreatment with other drugs might mitigate such undesirable effects on memory (Harper, 2013; Macaskill, Harrow, & Harper, 2015). Studies examining the effects of ongoing *chronic* drug treatment on delayed matching-to-sample performance are less common but have documented evidence of tolerance to the memory disruptive effects of illicit drugs, such as cocaine (Kangas & Branch, 2012). Forgetting functions derived from delayed matching-to-sample procedures can also be assessed for the ability of drug administration to improve short-term memory. Although the laudable goal of developing so-called cognitive enhancers has been elusive, there have been promising findings. For example, a compelling line of research examining administration of nicotinic and other pharmacologically-similar cholinergic ligands have revealed upward shifts in portions of the forgetting function (Buccafusco, Letchworth, Bencherif, & Lippiello, 2005; Elrod, Buccafusco, & Jackson, 1988); however, interpretive caution is required (Soto, Dallery, Ator, & Katz, 2013). Finally, the delayed matching-to-sample task has been effectively used in medications development to offer preclinical appraisals of candidate therapeutics with the goal of developing drugs that do not perturb short-term memory at doses that have medicinal value. Recent positive examples in nonhuman primates across diverse areas of study
include trace amine-associated receptor 1 agonists for narcolepsy treatment (Goonawardena et al., 2019), kynurenic acid for use in cannabis use disorder pharmacotherapies (Justinova et al., 2013), and the pseudoirreversible mu opioid receptor antagonist methocinnamox for conditions of opioid abuse and overdose (Minervini, Disney, Husbands, & France, 2020).

### 2.3.2 Self-ordered spatial search

The **self-ordered spatial search task**, like delayed matching-to-position, examines short-term spatial memory via the ability of a subject to remember spatial dimensions of stimuli presented. This task is based on the Hamilton search task (Hamilton, 1911) and the radial arm maze task (Levin, 1988), which was later adapted for use in human neuropsychological assessments (Owen, Downes, Sahakian, Polkey, & Robbins, 1990) and nonhuman primates using standard operant conditioning chambers (Levin & Bowman, 1986) and touchscreen-equipped chambers (Weed et al., 1999). In the prototypical touchscreen-based task variant, a subject is presented with a variable number of simultaneously available response boxes in different locations on the touchscreen. If the subject touches each of the response boxes once, and only once, reinforcement is delivered. Responding on a box that had already been touched in that trial terminates that trial without reward and leads to a timeout. Memorial processes are tested by introducing a variable delay (retention interval) after each box touch where all boxes disappear and then reappear in the same position, thus, requiring the subject to remember which have and have not been touched. Like delayed matching-to-sample and -position tasks, difficulty in the self-ordered spatial search task can be adjusted depending on subject performance by increasing the retention interval following each response and/or number of boxes presented in each trial. This task, often used as one component of a larger battery, has demonstrated value by elucidating deficits in spatial working memory following central nervous system dysfunction caused by simian immunodeficiency virus infection (Weed et al., 2004) or acute treatment with a variety of psychoactive drugs, including scopolamine (Levin & Bowman, 1986; Taffe, Weed, & Gold, 1999), ketamine (Taffe, Davis, Gutierrez, & Gold, 2002), dopamine antagonists (Von Huben et al., 2006), and Δ9-THC (Wright, Vandewater, & Taffe, 2013). Other studies in monkeys conducted over a year after a short-course but high dose MDMA treatment regimen exhibited substantial and lasting serotonergic depletion in several cortical regions without producing persistent deficits on several cognitive tasks, including in the self-ordered spatial search task (Taffe et al., 2002).
Interestingly, however, subsequent challenges with the mixed 5HT_{2A/2C} antagonist ketanserin, the 5HT_{2C} agonist 1-(3-Chlorophenyl)piperazine dihydrochloride, and the 5HT_{1A} agonist (±)8-hydroxy-DPAT hydrobromide significantly worsened five-choice serial reaction time (Section 2.4.2) and progressive ratio (Section 2.5.1) performance without perturbing self-ordered spatial search. This provides evidence that previous history with a drug associated with abuse liability and long-lasting neurochemical alterations will not necessarily have enduring deleterious effects on complex behavior, despite task-selective vulnerabilities to receptor-mediated physiologic challenges.

2.4 Attention

Systematic evaluation of a drug’s ability to enhance or impair attentional processes can serve as a metric of potential medicinal value in the case of the former or unwanted side-effects in the case of the latter. Although the discovery of pharmacologic enhancers of learning and memory has been elusive and often produce only ephemeral outcomes, the ability of a drug to extend sustained attention to task engagement has been repeatedly detected in animal models. This has been observed primarily with psychomotor stimulant drugs which, indicative of translational relevance, are employed successfully in the clinical management of attention deficit disorders. Like learning and memory tasks, animal models of attention also serve as valuable assessments of the extent to which a drug adversely affects the subject’s ability to maintain effective and efficient task performance. An understanding of which drugs (at which doses) can enhance or perturb performance that requires sustained vigilant responding can contribute to a comprehensive appraisal of their medicinal value.

2.4.1 Psychomotor vigilance

The psychomotor vigilance task, like all tasks highlighted in this chapter, has several procedural variants to assay sustained attention. However, many of the task elements can be traced back to studies from the 1940s, in which World War II service members were performing extended signal detection tasks, often tracking the movements of a clock (Mackworth, 1948) or blips on a radar screen (Anderson & Lindsley, 1944) which proved to have high translational relevance to mission success. Indeed, both Nazi Germany and the Allied Powers began experimenting with amphetamines and other psychomotor stimulants to extend battle-ready attentional processes and sustained vigilance during combat (Rasmussen, 2011). In a standard variant
of the psychomotor vigilance task, responses are reinforced following detection of a visual stimulus on a computer screen. The precise location, intensity, and duration of stimulus presentation can vary depending on the species, response, and experimental goals. However, reaction time thresholds are typically a primary dependent measure, which usually degrade following extended exposure to the task or environmental stressors such as sleep deprivation (Deurveilher, Bush, Rusak, Eskes, & Semba, 2015; Dinges et al., 1997). In the context of interconnected approaches designed to understand both drugs of abuse and candidate therapeutics, animal variants of the psychomotor vigilance task are devised to reveal the extent to which a drug can either worsen attentional processes, improve them via slowing its time-dependent degradation, or enhance wakefulness following conditions of sleep deprivation (McCarthey et al., 2017). Not surprisingly, administration of drugs such as Δ⁹-THC in monkeys produced dose-related decrements on sustained vigilance (Kangas et al., 2016); however, studies with relatively low doses of the psychomotor stimulants caffeine, nicotine, cocaine, and amphetamine in rats documented systematic improvements in task metrics (Davis, Roma, & Hienz, 2016; Evenden, Turpin, Oliver, & Jennings, 1993) similar to findings observed in human studies (Silber, Croft, Papafotiou, & Stough, 2006).

2.4.2 Five-choice serial reaction time

The five-choice serial reaction time task shares several characteristics with the psychomotor vigilance task but also has distinct features to assay attentional processes. Rather than responding to stimuli on a computer screen, the five-choice serial reaction time task is typically conducted in specialized chambers designed for rats and mice and include five transilluminated nose-poke apertures. In its typical arrangement, one of the five nose-poke apertures is illuminated for an interval that can vary in difficulty by its duration or brightness and by requiring a response within a very limited duration for reward. Task performance can be evaluated by analyzing session-wide hits, misses, premature responses, and response omissions. Although sometimes used to probe impulse control (see Section 2.6), the development of this task originally stemmed from studies examining attentional processes related to attention deficit disorders via lesion and drug studies in rats (Carli, Robbins, Evenden, & Everitt, 1983; Robbins, 2002). Subsequent use of this task has highlighted its value across drug classes, including documenting adverse effects on attentional processes following treatment with amphetamine (Cole & Robbins, 1987), scopolamine (Jones & Higgins, 1995; Shannon & Eberle, 2006), to a lesser extent...
morphine (Maguire, Henson, & France, 2016; Pattij, Schetters, Janssen, Wiskerke, & Schoffelmeer, 2009), and during both cocaine and heroin withdrawal (Dalley et al., 2005). Consistent with their attention-enhancing profile, low doses of nicotine, caffeine, and amphetamine have been shown to enhance accuracy and other performance metrics in this task (Bizarro, Patel, Murtagh, & Stolerman, 2004; Grottick & Higgins, 2002; Stolerman, Mirza, Hahn, & Shoib, 2000). Finally, this task has also served an innovative role in medications development, for example, in studies examining the ability of orexin/hypocretin antagonists to reduce cocaine-induced premature responding as a behavioral marker of drug-induced deficits in executive functioning (Gentile et al., 2018).

2.5 Motivation

It is well known that motivation can be increased or decreased by psychoactive drugs. One common approach to studying drug effects on motivational processes in laboratory animals is to examine how pharmacological treatment modifies responding for an appetitive consequence, for example, a palatable food reward. After establishing stable baseline consumption, subsequent drug administration can probe whether the rate of operant responding increases, decreases, or is unaffected, with the assumption that dose-related changes in responding reflect pharmacological mediation of reward value. Another common approach to studying motivation is to examine the conditions under which a subject will respond for the drug itself. In this case, self-administration procedures can be arranged to derive the relationship between response output and unit dose, which can serve as an index of motivational limits for procurement of a given drug dose.

2.5.1 Progressive ratio

The progressive ratio task has been used for decades to examine motivational processes via how much a laboratory animal will respond for a given reinforcer (Hodos, 1961). In its standard arrangement, a subject will respond on a lever or other operandum under a ratio schedule of reinforcement with a small response requirement for the first reward. The response requirement subsequently increases following each reward delivery until the subject ceases to respond for some pre-determined period of time. The largest response requirement completed defines the break point and this value serves as a primary dependent measure. As with all behavioral assays, parameters in the progressive ratio task (e.g., ratio step-size, break-point criteria, reinforcer magnitude) can influence outcomes and should be carefully selected and, preferably, accompanied with control studies using varied procedural
parameters to increase interpretive confidence in the data’s predictive relevance to constructs of motivation (Bradshaw & Killeen, 2012; Stafford & Branch, 1998). Caveats aside, the progressive ratio task has been used in numerous studies to examine how drugs modify response output for palatable food rewards (Higgins et al., 2021; Kangas et al., 2016; Slezak, Desai, & Katz, 2017) and to determine the relative reinforcing effectiveness for administration of drug rewards across diverse classes, including the exploration of GABA_A receptor subtypes in the reinforcing effects of benzodiazepines (Berro & Rowlett, 2020), the mitigating factors of exercise in the abuse potential of speedballs (Lacy, Strickland, Brophy, Witte, & Smith, 2014), and sex differences in addiction-like behavioral phenotypes during cocaine withdrawal (Towers, Bakhti-Suroosh, & Lynch, 2021). In addition, progressive ratio tasks have been used to appraise candidate therapeutics in innovative ways. For example, atypical dopamine uptake inhibitors have been studied with respect to anergia in rat progressive ratio performance with an aim to develop novel treatments for motivational dysfunction (Rotolo et al., 2019). In addition, chronic treatment of bupropion-like dopamine reuptake inhibitors have been examined as candidate nicotine-replacement agents designed to aid in nicotine cessation via the reduction of progressive ratio break points in nicotine self-administration (Coen, Adamson, & Corrigall, 2009).

2.5.2 Economic demand

The economic demand task and associated quantitative metrics are designed to capture similar features of motivation for reward as those assayed under the progressive ratio task. However, in economic demand tasks, a given response requirement for reward is typically varied across sessions or, in within-session task variants, across fixed-time components. Motivation is quantified by examining the number of rewards earned under a variety of response requirement conditions using equations derived from behavioral economics. In its most popular iteration, Hursh and Silberberg (2008) promulgated the following exponential demand equation that has been employed by a considerable number of empirical investigations:

\[
\log Q = \log Q_0 + k\left(e^{-aQ_0C} - 1\right)
\]

where \( Q \) is quantity consumed, \( Q_0 \) is consumption as price approaches 0 (baseline consumption), \( k \) is a constant representing the range of consumption in log units, \( a \) is the rate of change in consumption as price goes...
up (elasticity), and $C$ is cost (response requirement). In addition to avoiding certain shortcomings of the progressive ratio task, for example, response requirement sequence effects (Maguire, Minervini, Dodda, & France, 2020), this quantitative framework allows for interrogation of different aspects of motivation for reward. For example, the equation can distinguish between a subject’s response output for reward when costs are near-zero ($Q_0$) and the extent to which a subject will defend its levels of reward consumption as costs increases (elasticity or $\alpha$). Importantly, task and equation variants continue to be developed to better model economic demand data (Koffarnus, Franck, Stein, & Bickel, 2015). Nevertheless, a close conceptual correspondence already has been successfully demonstrated for this quantitative framework in research with laboratory animals and humans (Strickland & Lacy, 2020) to examine motivation to respond for, and associated reinforcing effectiveness of, a variety of commonly abused drugs, including cocaine (O’Connor, Aston-Jones, & James, 2021), ethanol (Kim & Kearns, 2019), fentanyl (McConnell et al., 2021), and nicotine (Powell, Beckmann, Marusich, & Gipson, 2020), to name just a few recent examples.

2.6 Impulsivity

Impulsivity as a construct has been well-associated with drug use and abuse (Jentsch et al., 2014; Perry & Carroll, 2008). A highly active and provocative debate continues as to whether individuals with substance use disorders are more impulsive than healthy controls (trait theory) or if drug exposure itself can decrease levels of self-control (state theory). Although the nuances of this debate are beyond the scope of the present chapter and are offered elsewhere (de Wit, 2009; Odum, 2011), there are several diverse tasks that can assist in contributing to this important topic. In addition to the tasks highlighted below, it should be noted that the discrimination reversal task (Section 2.2.1) and five-choice serial reaction time task (Section 2.4.2), which were described above in the context of their ability to probe cognitive flexibility and attention, respectively, are also highly relevant to impulsivity insomuch as deficits in response inhibition have been associated with indices of impulsive behavior and drug addiction (Izquierdo & Jentsch, 2012; Smith, Mattick, Jamadar, & Iredale, 2014).

2.6.1 Stop signal task

The stop signal task is another paradigm originally developed in the human laboratory (Logan & Cowan, 1984), subsequently used in the clinic to
characterize impulse control disorders (Aron & Poldrack, 2005), and reverse-translated for rats (Eagle & Robbins, 2003) and monkeys (Liu, Heitz, & Bradberry, 2009) to yield effective coordinated and bi-directional cross-species methods in medications development (Robbins, 2017). The stop signal task, also known as the go/no-go task, assays motoric impulsivity by measuring the amount of time to respond in the presence of a “go” stimulus or, alternatively, inhibit a response after it has been initiated (i.e., the ability to stop) following subsequent presentation of a “stop” stimulus. For example, a trial-initiating response is required first, followed by presentation of a “go” stimulus (e.g., a green light) after a variable delay. Responding quickly within a narrowly defined window of time (limited hold) results in reward. However, in a minority of trials, a “stop” stimulus (e.g., a tone) is presented after the “go” stimulus, which signals that inhibition of the prepotent response is required to obtain reward. Following sufficient training, a negative correlation is observed between the stop signal delay and performance accuracy, with a zero-delay producing high levels of response inhibition and longer delays producing lower stop accuracies. Impulsivity in this context is defined by a subject requiring extended training, relative to normative outcomes under the conditions arranged, to successfully inhibit responding following stop signals. Impulsivity is also associated with an increase in reaction time on trials following stop signal trials (i.e., post-stop trial slowing). In addition to the rich literature using this task to characterize the neurobiology of response inhibition (Bari & Robbins, 2013) and attention deficit disorders (Alderson, Rapport, & Kofler, 2007), other studies have used this task to examine drugs of abuse. For example, findings in monkeys with an extensive history of cocaine intake, but during forced-abstinence conditions, revealed longer stop signal reaction times and lower post-stop trial slowing (Liu et al., 2009). This impulsive phenotype is highly consistent with studies of impulsivity deficits in chronic cocaine users (Fillmore & Rush, 2002). Other studies using the stop signal task have documented that amphetamine and methylphenidate increase both premature responding and responses after the stop signal, whereas atomoxetine produced small performance enhancements on stop signal accuracy and reduced premature responding in rats (Maguire & France, 2019), consistent with its medicinal profile as an effective treatment for attention deficit disorders in humans.

2.6.2 Delay discounting

The delay discounting task is designed to assay another distinct aspect of impulsivity, namely, impulsive choice, and represents yet another task that
includes tailored variants for both humans and laboratory animals to foster coordinated and bi-directional research aimed at understanding how psychoactive drugs, among numerous other variables, modulate this fundamental behavioral process (Madden & Bickel, 2010). This paradigm has in recent years generated substantial interest and numerous procedural variants. However, at its core, a delay discounting task assays the rate at which a given reward is devalued as a function of time, with the rate of decay serving as a primary dependent variable. This can be measured by arranging conditions that allow the subject to repeatedly choose between smaller magnitude rewards delivered sooner and larger magnitude rewards delivered later. Protocols that titrate the delay but hold reward magnitudes constant (Mazur, 1987) or titrate the reward magnitude but hold delays constant (Richards, Mitchell, de Wit, & Seiden, 1997) are aimed at defining *indifference points*, which can be compiled across a parametric space to derive a subject’s discounting function. Discussions regarding how best to fit these functions, for example, exponential vs hyperbolic curves (Madden, Bickel, & Jacobs, 1999; McKerchar et al., 2009), provide important insights into the nature of the behavioral process. Notwithstanding these debates, subjects that reliably demonstrate preference for smaller-sooner rewards over larger-later rewards are deemed more impulsive relative to subjects that reliably choose larger-later rewards over smaller-sooner rewards and are deemed self-controlled (Ainslie, 1974). In the context of this chapter, two fundamental uses of this task are to better understand how drug exposure can modify discounting processes for other rewards and, as well, how drugs as the rewards themselves are discounted (Heyman, 2009; Lamb, Maguire, Ginsburg, Pinkston, & France, 2016; Setlow, Mendez, Mitchell, & Simon, 2009). Indeed, highly robust observations of steeper discounting functions have been associated with substance use disorders in humans across multiple drug classes (Bickel et al., 2020). In addition, delay discounting studies in laboratory animals have revealed functional similarities in heightened impulsivity metrics following exposure to alcohol (Poulos, Le, & Parker, 1995), cocaine (Perry, Nelson, & Carroll, 2008), d-amphetamine (Cardinal, Robbins, & Everitt, 2000), and nicotine (Dallery & Locey, 2005). Effects of opioid treatment on delay discounting tasks in rats, however, have produced mixed findings with some studies documenting the inability of chronic heroin intake to modulate discounting functions for a food reward (Harty, Whaley, Halperin, & Ranaldi, 2011). Whereas other studies have shown that morphine-dependent rats had increased measures of impulsivity for a food reward, relative to drug-free
control subjects, that subsequently subsided following abstinence (Harvey-Lewis, Perdrizet, & Franklin, 2012). In nonhuman primates, both acute and daily morphine administration were associated with individual differences in their capacity to increase impulsive choice for a food reward (Maguire, Gerak, & France, 2016). It may be fruitful to consider viewing these inconsistencies and individual differences in sensitivity to the effects of opioids on delay discounting in the context of a potential preclinical indicator of vulnerability for drug abuse, given functional similarity to this phenomenon observed in humans (Madden, Petry, Badger, & Bickel, 1997).

3. Caveats and considerations

It is worth remembering that the enterprise of behavioral pharmacology was largely founded on systematic evaluations of drug effects on scheduled-controlled operant behavior (Dews, 1955; Kelleher & Morse, 1968). Although it is common to describe cognitive tasks as complex, each task highlighted in this chapter can be distilled to chained operant arrangements, with schedules of reinforcement serving as their backbone. As such, each link in the chain can itself have complex control over behavior. Indeed, even simple schedules of reinforcement are only simple insomuch as they are easy to describe; however, their effects on behavior and as determinants of drug action can nevertheless be exceedingly complex (Ferster & Skinner, 1957; McKearney & Barrett, 1978).

In addition, every psychoactive drug by its categorical nature will produce non-specific effects on behavior at some dose. Therefore, when examining drug action on these and other cognitive tasks, it is worthwhile to interrogate each link in the chain and attend carefully to how a drug selectively (or non-selectively) modifies each procedural variable that comprises the assay. An example from the repeated acquisition literature is instructive. For the reasons discussed in Section 2.1.1, one might arrange the conditions for a laboratory animal to learn new visual discriminations daily. Following stability in acquisition rate, if pre-session drug treatment dose-dependently increases the number of trials required to master a novel discrimination, an obvious conclusion is that the drug adversely affected learning processes. However, a skeptic might wonder whether the drug impaired the ability of the subject to learn something new or if the drug had non-specific behavioral effects that hindered the ability of the subject to engage in the task and demonstrate whether it was able to learn something new. This distinction is subtle but nonetheless crucial. One solution is to test this competing
hypothesis by modifying the repeated acquisition task to include probe trials that are intermittently programmed throughout the daily session, for example, every 10 trials, in which the subject is presented with the same $S^+/S^-$ stimuli they have a long and accurate history discriminating. Then, task performance during sessions following drug treatment can be juxtaposed using accuracies during probe trials with accuracies during trials using novel stimuli. If a drug adversely affects discriminative performance during trials with novel stimuli but not during probe trials, one may conclude the dose selectively impaired the subject’s ability to learn a new discrimination but not necessarily its ability to discriminate. This particular approach already has been shown to successfully appraise selectivity in discrimination learning studies with MDMA, methamphetamine, and methylphenidate in rats (Galizio, McKinney, Cerutti, & Pitts, 2009) and cannabinoid agonists in monkeys (Kangas et al., 2016).

Another tactic to help elucidate selectivity in drug action on complex behavioral processes is to examine a drug under a battery of diverse cognitive tasks. As discussed in detail elsewhere (Bussey et al., 2008; Dumont et al., 2021; Kangas & Bergman, 2017), the flexibility inherent in touch-sensitive apparatus allows for the ability to expose laboratory animals to a variety of tasks, including all of those highlighted in the present chapter. However, whether using touchscreen-based or traditional operant conditioning chambers, examination of the same drugs at the same doses across diverse tasks allows for measurement of selectivity in a drug’s ability to produce desirable or undesirable effects on various behavioral endpoints. The extent to which relevant drug doses impact certain task performances but not others provide critical verification of selective impact on some but not all behavioral outcomes, thereby affirming the drug is not simply decreasing the probability, rate, or accuracy of all responding. This approach also provides an important way to rank drugs designed for the same medicinal target.

4. On terms coda

Although discussing cognitive tasks in regard to their ability to assay so-called cognitive function may serve descriptive ends, it is nevertheless important to maintain focus on precision in operational definitions. And while it is linguistically convenient to have task types (nouns) to categorize task performance (verbs), one should not fall into the trap of confusing the contingencies arranged and dependent measures studied with their associated hypothetical constructs that should serve only as shorthand.
Perhaps the most cogent warning was offered 100 years ago in one of the first psychology textbooks:

Instead of “memory” we should say “remembering”; instead of “thought” we should say “thinking”; instead of “sensation” we should say “seeing, hearing,” etc. But, like other learned branches, psychology is prone to transform its verbs into nouns. Then what happens? We forget that our nouns are merely substitutes for verbs, and go hunting for the things denoted by the nouns; but there are no such things, there are only the activities that we started with, seeing, remembering, and so on. Intelligence, consciousness, the unconscious, are by rights not nouns, nor even adjectives or verbs; they are adverbs. The real facts are that the individual acts intelligently—more or less so—acts consciously or unconsciously, as he may also act skillfully, persistently, excitedly. It is a safe rule, then, on encountering any menacing psychological noun, to strip off its linguistic mask, and see what manner of activity lies behind.

Woodworth (1921, p. 5–6)

Here, Woodworth presents the hazards of reification when discussing cognition and we encounter a thorny affair when studying behavior. Our constrained linguistic structure presents limitations in talking about process and activity. The structure of Western languages, including English, necessitates segmenting the world around us into categories of verbs that require their organization around nouns. These arbitrary segmentations that imply discrete, unidirectional actions across time, instead of ongoing, multiply determined processes, likely contribute to obfuscation of the dynamics of behavioral processes. To be sure, as behavioral pharmacology continues to progress, we will need categorical terms to help elucidate the complicated, multifaceted, and fluid nature of drug/behavior interactions. And some of those words will necessarily have to be nouns. It is commonplace and, under some circumstances, useful shorthand to specify drugs that might, for example, impair memory, improve attention, or foster cognitive flexibility. However, as this early comment by Woodworth emphasizes, a fastidious focus on activity will help avoid confusing our subject matter with the words we must use to describe it.

5. Conclusion

As the numerous and diverse tasks highlighted in this chapter show, empirically validated methods have been developed for laboratory animals that include tailored variants for the species, drug class, and experimental questions required to illuminate the many intricacies of drug action on complex behavioral processes. These tools have proven effective in
advancing our understanding of both abused drugs and candidate therapeutics. Moreover, considerable value has been added via coordinated bi-directional translational research with functionally similar tasks in human subjects. These extant tasks, along with the continued development of innovative paradigms stemming from clinical observations and laboratory discoveries, will be needed to both minimize existing knowledge gaps regarding drug abuse sequela and improve pharmacotherapeutic treatment options for various medical conditions.

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