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Drug Discrimination and the Analysis of Private Events

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Abstract

A defining feature of radical behaviorism is the explicit inclusion of private events as material phenomena within a science of behavior. Surprisingly, however, despite much theorizing, there is a notable paucity within behavior analysis of controlled experimentation and analysis of private events, especially in nonhuman animals. One technique that is amenable to the study of private events is drug discrimination. For over 40 years, drug discrimination procedures have been an incredibly effective tool providing a wealth of *in vivo* pharmacological information about drugs including receptor selectivity, potency, and efficacy. In addition, this procedure has provided important preclinical indications of abuse liability. However, despite its prowess as a pharmacologic tool, or perhaps because of it, empirical investigation of its parameters, procedural elements, and variants is not currently an active research domain. This review highlights the drug discrimination procedure as a powerful means to systematically investigate private events by using drugs as interoceptive stimuli. In addition to the opportunity to study privacy, empirical evaluation of the drug discrimination procedure will likely inform and improve the standard practice for future endeavors in basic and clinical pharmacology.

Keywords

drug discrimination; private events; radical behaviorism; behavioral pharmacology

Private Events

In his landmark paper, *The Operational Analysis of Psychological Terms*, Skinner (1945) defined radical behaviorism largely by the emphasized inclusion of private events within a natural science of behavior (see also Skinner, 1953; 1957; 1963; 1974). Private events are behavioral phenomena (e.g., stimuli and responses) occurring covertly inside the skin, consisting of sensations such as pain, taste, and smell as well as behavior such as feeling, thinking, and imagining. Skinner noted that this treatment of private events is a primary point of departure of his version of radical behaviorism from the so-called methodological behaviorism which was, and continues to be, a dominant view in the behavioral sciences. He and others (Day, 1983; Leigland, 2014; Marr, 2011; Moore, 1980; Palmer, 2009; Schnaitter, 1978; Zuriff, 1979) made clear that private events are not merely physiological mediators or

mental precursors of overt behavior. That is, they are not the *inner causes* of behavior in the colloquial sense that one thinks before he acts or senses pain before he flinches. Instead, private events are behavioral phenomena in their own right and should to be subjected to rigorous behavioral analysis like those involving public stimuli and responses. The problem with privacy, however, is that controlling stimuli are not readily observable to others.

Skinner suggested some ways in which private events may establish control over public behavior. For example, stimulus control may be established by a verbal community that effectively uses *public accompaniments* of private stimuli to differentially reinforce appropriate behavior. He asserted, "...one may teach a child to say 'That hurts' in agreement with the usage of the community by making the reinforcement contingent upon public accompaniments of painful stimuli (a smart blow, tissue damage, and so on)" (Skinner, 1945, p. 273). An important goal of a science of behavior is to understand the necessary and sufficient conditions under which such behavior is established and maintained.

There is apparent consensus within contemporary behavior analysis regarding the importance of Skinner's theorizing (e.g., special sections in the Fall 2011 issue of *The Behavior Analyst* and the 2009 issue of *Behavior and Philosophy*). However, empirical study of privacy appears to be moribund. As Palmer (2011) noted, when scientific phenomena of interest are not easily observed (e.g., planets before the invention of telescopes), the transition from theory to empirical analysis can be slow. Private events, by definition, are not readily observed by others and, therefore, must be inferred. Inferences can be a particularly thorny issue, especially within a science of behavior that values objective and reliable measurement of behavior and its controlling variables. That is not to say no progress has been made. Indeed, the behavior analytic research subdomain of verbal behavior has continued Skinner's (1957) analysis and, as any recent issue of the *Analysis of Verbal Behavior* will highlight, empirical study of verbal operants is an active line of inquiry that can be pertinent to private events. However, by design, these studies most often focus on language in human subjects and, therefore, the findings will likely remain limited in scope and species. Moreover, considering the complexity of the privacy problem, it will be useful to employ multiple empirical techniques.

In summary, it is surprising that the science of behavior analysis, so heavily influenced by its radical behaviorist philosophy, has not more actively studied private events in the laboratory. One approach to the study of privacy that can be conducted under controlled conditions, and in both human and nonhuman animals, is drug discrimination. Because this approach is perhaps underappreciated in behavior analysis, the purpose of this review is to provide an overview of the drug discrimination procedure, consider its unrealized potential in the study of privacy, and highlight some future directions.

Drug Discrimination

Empirical assessment of private events is not a particularly straightforward endeavor given problems of accessibility. However, as others have previously noted (Branch, 2006; DeGrandpre, Bickel, & Higgins, 1992; Lubinski & Thompson, 1987), research in drug discrimination provides a feasible and potentially fruitful approach to the study of privacy.

For over 40 years, drug discrimination procedures have been an incredibly effective tool, providing *in vivo* pharmacologic measures of behaviorally-active drugs including receptor selectivity, potency, efficacy, as well as indications of abuse liability, and has been used to characterize aspects of a wide range of so-called *subjective effects* of drugs, initially thought too private to characterize (reviewed in Glennon & Young, 2011; McMahon, 2015; Preston & Bigelow, 1991; Schuster, Fischman, & Johanson, 1981).

Under drug discrimination procedures, administration of a drug produces an interoceptive stimulus. This interoceptive stimulus can be trained to serve as a discriminative stimulus through differential reinforcement in much the same way as exteroceptive stimuli, such as lights or tones. For example, prior to some sessions, the training drug is administered and responding on one lever (drug lever) is reinforced; prior to other sessions, an inert vehicle (e.g., saline) is administered and responding on the other lever (vehicle lever) is reinforced. Drug and vehicle are administered with the same pretreatment time and through the same route of administration in order to control for factors related to drug delivery. After sufficient training, differential responding emerges in which subjects respond reliably on the drug lever following drug administration and on the vehicle lever following vehicle administration.

Figure 1 presents idealized drug discrimination data to illustrate common outcomes. The circles left of the abscissa break represent near-0% and near-100% of total responding on the drug lever following administration of the vehicle (V) and the training dose (TD), respectively, indicative of performance under training conditions in well-trained subjects. Thousands of drug discrimination studies have demonstrated that this sort of discrimination using an interoceptive drug stimulus can be effectively established and maintained in a variety of species including rodents, birds, monkeys, and humans. That such stimuli can serve as a discriminative stimulus with the same effectiveness as an external stimulus like a light or tone provides definitive evidence that behavior can come under control of interoceptive stimuli.

One of the primary features of drug discrimination that makes it so useful is its ability to elucidate the similarities and differences in the pharmacology of drugs. Two important dimensions of a drug's effects are potency (the doses of drug required to produce particular levels of effect) and efficacy (maximal effect). Drug discrimination allows for *in vivo* quantification of effects along both dimensions. Subjects trained to discriminate a drug will readily respond on the drug lever following administration of the training drug, but not all doses produce the same magnitude of effect. Although there are some important caveats noted below, small doses of the training drug typically occasion responding on the vehicle lever, and increasing doses of the training drug dose-dependently increase the percentage of drug lever responding (Figure 1, circles right of the abscissa break). Interestingly, drug discriminative stimuli appear to share similarities with non-drug discriminative stimuli in their control of behavior. For example, generalization gradients comprised of the ascending dose-effect curve often resemble the left-half of generalization gradients generated with visual stimuli varying in some physical property such as wavelength (cf. Blough, 1967; Kangas et al., 2013).

After the discrimination with the training drug has been established, drugs other than the training drug can be tested, essentially asking the subject if a test drug is *like* the training dose of the training drug or not. Test drugs that occasion drug lever responding are said to generalize to (some say substitute for) the training drug and the proportion of response allocation on the drug lever is the index of generalization (i.e., partial vs. full). Test drugs that generalize can vary in potency, represented in Figure 1 by the upright triangles and inverted triangles showing full generalization with, respectively, higher and lower potency relative to the training drug. For example, in some cases a drug might occasion a full effect, but do so at smaller doses (upright triangles). Evaluating the potency of a test drug in this manner can provide useful preclinical information in regards to the range of doses which would be expected to produce effects like those of the training drug. In addition, drug discrimination procedures can provide information about a drug's relative efficacy. Drugs that interact at the same receptor often vary along a continuum in the degree to which they activate that receptor. Some drugs produce a high-intensity response (full agonists), others produce an intermediate-intensity response relative to a full agonist (partial agonists), and still others bind to the receptor but produce no response at all (antagonists). It is often the case that if the training drug acts as a full agonist at a receptor, generalization tests with other full agonists will occasion near exclusive responding on the drug lever, but partial agonists will occasion mixed response allocation across the drug and vehicle levers, indicative of partial generalization to the training drug (Colpaert & Janssen, 1984). This partial agonist profile is idealized by the squares in Figure 1. Whether test drugs produce responding consistent with a full- or partial-agonist profile depends upon many factors including the dose of the training drug (Colpaert, Niemegeers, & Janssen, 1980). Importantly, there is often a high correlation between these *in vivo* assessments of potency and relative efficacy and *in vitro* techniques (Picker et al., 1993; Traynor & Naharski, 1995).

Another consideration in understanding the discriminative stimulus effects of a drug is to determine which drugs fail to generalize to the training drug. These *negative controls*, idealized by the diamonds in Figure 1, provide information regarding the selectivity of the interoceptive training stimulus. Most often, drugs that interact at the same receptor(s) with similar actions (e.g., agonism) as the training drug categorize well which drugs will generalize and drugs that do not interact with the receptor(s) in the same manner will not, thus providing a behavioral model that yields highly predictive information related to another level of analysis, i.e., receptor signaling systems within the central nervous system. For example, in subjects trained to discriminate an agonist at the mu opioid receptor such as morphine, administration of drugs that bind to, but do not activate, the mu opioid receptor, e.g., antagonists such as naloxone, fail to occasion drug-lever responding (Shannon & Holtzman, 1976). Likewise, discriminative specificity is often high when examining differences in receptor subtypes, even when drugs that activate different subtypes share some behavioral effects. For example, the opioid system is intricately involved in the sensation of pain. Opioid receptors can be divided into three distinct classes: mu, kappa, and delta. Generally speaking, agonists that activate the mu-opioid and kappa-opioid receptor subtypes have antinociceptive effects (i.e., they attenuate pain sensation) that are remarkably similar in behavioral assays related to pain (Millan 1989; 1990). However, other effects are not shared; for example, mu-opioid receptor agonists cause pruritus whereas kappa-opioid

agonists do not (Ko et al., 2004) and kappa-opioid agonists cause diuresis whereas mu-opioid receptor agonists do not (Dykstra et al., 1987). Drug discrimination provides a tool for studying these differences. When the training stimulus is the mu-opioid receptor agonist morphine, subjects will reliably respond on the drug lever following administration of other mu-opioid receptor agonists (e.g., methadone, oxycodone, and heroin). However, administration of kappa-opioid receptor agonists like U50,488 or bremazocine will typically produce responding on the vehicle lever, thereby reporting effects as not morphine-like (Picker & Dykstra, 1987). Thus, even though mu-opioid and kappa-opioid receptor agonists act at subtypes of the same family of receptor and share some effects, drug discrimination is able to elucidate the pharmacology underlying other differences in their discriminative effects.

Finally, in a clinically-relevant use of this assay, drug discrimination provides preclinical evidence regarding a drug's abuse liability which has been especially critical in the evaluation of new pharmacotherapies (Ator & Griffiths, 2003). For example, if a candidate therapeutic drug is suspected to have potential for abuse on the basis of its *in vitro* pharmacology, the Food and Drug Administration will often require the pharmaceutical company to provide drug discrimination data during early stages of the approval process to determine whether the candidate drug shares discriminative stimulus effects with known drugs of abuse. Likewise, the Drug Enforcement Agency often considers drug discrimination data when determining scheduling under the Controlled Substance Act (Mansbach et al., 2003). Generalization to a known drug of abuse is often highly predictive of the extent to which the test drug will also be abused and, interestingly, aligns with self-administration procedures in the assessment of abuse liability in some circumstances (Woods, Winger, & France, 1992).

Future Directions

Returning to Skinner's radical behaviorism and the framework under which privacy operates, drug discrimination would likely be useful for understanding important aspects of functional relationships between private stimuli and public accompaniments. As noted by Branch (2006),

“The drug-discrimination procedure models some interesting features of the interpretation offered by Skinner. In a sense, the experimenter serves as the animal's *verbal community* by reinforcing correct responses and extinguishing incorrect ones. Experimenters have access to the public accompaniments of the drug state in the sense that they know what was injected, whether drug or vehicle. The experimenter does not, however, have access to the private stimuli generated by drug administration. Just as with human learning about private events, therefore, the contingencies are arranged in accord with the public accompaniments, with the hope that they correspond to private stimuli. Successful training of a discrimination is validation that they do” (p. 412).

The contribution of drug discrimination to understanding the *in vivo* pharmacology of behaviorally-active drugs can hardly be overstated; thousands of empirical studies attest to its utility. However, it is also clear that drug discrimination remains an untapped resource

when it comes to understanding more about behavior generally and private events specifically and many fertile avenues of research likely exist. For example, important private phenomena that have high clinical relevance are the private events associated with withdrawal in drug-dependent subjects. Drug abuse involves repeated drug taking, often over long periods of time. Repeated administration of some drugs can lead to the development of physical dependence which is revealed by the emergence of withdrawal symptoms following abstinence. Withdrawal is thought to contribute to the persistence of drug use and the failure to maintain drug abstinence (Koob et al., 1989); however, many features of this complex phenomenon are not well-understood. The drug discrimination paradigm has been a useful tool for studying effects associated with withdrawal and thus has helped to elucidate some factors that might contribute to continued drug abuse. This is accomplished in the laboratory by first chronically-treating a subject with an agonist to establish dependence and then, under ongoing chronic-dosing conditions, training a discrimination using the interoceptive stimulus effects of a selective antagonist which displaces the agonist from its active site (France & Woods, 1989; Gellert & Holtzman, 1979; Gerak & France, 1999). In *antagonist drug discrimination*, the drug lever is associated with administration of the antagonist and therefore the absence of the chronically-delivered agonist from the receptor, whereas the vehicle lever is associated with administration of an inert vehicle thereby allowing the subject to report unperturbed discriminative stimulus effects of the ongoing chronic agonist administration.

In subjects dependent on certain drug classes (e.g., opioids, benzodiazepines), administration of the antagonist rapidly precipitates withdrawal symptoms similar to those that would be observed following drug abstinence, such as emesis, tremor, sleep disturbance, etc. (Becker et al., 2008; Lukas & Griffiths, 1982). An important validation that antagonist drug discrimination is modeling features relevant to withdrawal syndromes is demonstrated by the fact that discontinuing chronic agonist exposure typically produces an orderly shift of response allocation to the antagonist lever (sans antagonist) across a timeframe consistent with the pharmacokinetics of the agonist. This provides good evidence that the discriminative stimulus effects of antagonist-precipitated withdrawal generalize to the private events associated with drug abstinence. Importantly, not all drugs of abuse result in overt (public) symptoms of withdrawal following abstinence. Nevertheless, antagonist drug discrimination can be useful to examine more subtle (private) withdrawal symptoms that may occur without obvious public accompaniments. For example, McMahon and France (2003) chronically treated nonhuman primates with Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the primary psychoactive ingredient in marijuana. Under these chronic conditions, they were able to train rimonabant (a selective cannabinoid receptor antagonist) as a discriminative stimulus and, subsequently, observed antagonist-lever responding following discontinuation of chronic Δ^9 -THC in the absence of other public signs of withdrawal. Recent preclinical studies have used this approach to evaluate the effectiveness of candidate treatment drugs designed to alleviate putative symptoms of Δ^9 -THC withdrawal, evident in this paradigm by the extent to which treatments shift response allocation away from the antagonist lever following the discontinuation of chronic Δ^9 -THC (Stewart & McMahon, 2010). More generally, it is worth considering that in addition to the well-known positive reinforcing effects of drugs of abuse, negative reinforcement in the form of escape/avoidance of

withdrawal symptoms can also play an important role in addiction (Wise & Koob, 2014). In particular, the private events associated with withdrawal are critical features relevant to the important public health concern of drug relapse. However, these private events may not be homogenous or equivalent in their negative reinforcing strength. Systematic empirical analysis of these behavioral phenomena using antagonist drug discrimination would likely be a fruitful avenue of research with significant implications to addiction disorders.

When considering other future directions, an interesting contrast in juxtaposition is provided by the literature of delay discounting. The contemporary delay discounting procedure (Ainslie, 1975; Rachlin & Green, 1972) was promulgated at about the same time as the contemporary drug discrimination procedure (Barry, 1974; Colpaert, et al., 1975a; 1990b; c). Like drug discrimination, delay discounting procedures are also powerful and commonly employed techniques for a different end, namely, to identify causal and correlate variables related to impulsive choice (Odum, 2011). An increased understanding of delay discounting as a behavioral process, particularly during the last decade, has improved and expanded the paradigm to effectively address questions in a myriad of research domains ranging from drug abuse to gambling to obesity and beyond (reviewed in Madden & Bickel, 2010). This has been aided, in part, by recent technical and procedural advances such as quantitative modeling to describe the shape of the discounting function (Mazur & Biondi, 2009), examination of task exposure and reliability of the discounting function (Koffarnus & Bickel, 2014), ascending vs. descending sequences of delay (Maguire et al., 2014; Robles & Vargas, 2008; Tanno et al., 2014), and fixed vs. titrating sequence procedures (Rodzon, Berry, & Odum, 2011). The delay discounting field has benefited from expansion to other domains and subsequent refinement of the methodology to address a broader array of questions.

Curiously, however, examination of comparable elements of the drug discrimination procedure has not been as active of a research domain and it may be due to the fact that drug discrimination has been used nearly exclusively as a tool for understanding *in vivo* pharmacology. Although some basic parameters of drug discrimination have been systematically studied such as training dose (Stolerman et al., 2011) and >2 concurrent choice (Li & McMillan, 2001; Overton, 1982; Walker, Picker, & Dykstra, 2001), empirical investigations of other basic procedural elements remain incomplete. For example, most drug discrimination procedures with nonhuman animal subjects program small fixed-ratio (FR) schedules of reinforcement. However, the contingencies of reinforcement used in training and test sessions may influence response allocation on the levers. It has been known for some time that schedules of reinforcement can influence the effects of drugs on behavior (Dews, 1955), so it seems likely that the schedules used to *report* drug effects could also play a key role. In fact, scheduling may fundamentally alter the shape of the generalization dose-response function. For example, many drug discrimination studies use FR schedules and mixed response allocation across drug and vehicle levers is rare. Instead, subjects most often make quantal yes/no responses during generalization tests and the graded dose-response functions are mere artifacts of averaging across individual subjects that vary in sensitivity to the training dose (Colpaert, 1991; Stolerman, 1991). Interestingly, parallel artifacts often exist with other stimulus classes/modalities such as light intensity and tone frequency, calling into question the very existence of a continuous relation between

dimensions of stimulus intensity and operant response strength (reviewed in Bickel & Etzel, 1985). The extent to which this is a fundamental characteristic of behavior under the control of drug discriminative stimuli or an outcome of the particular training parameters remains unclear. The few drug discrimination studies that have used variable ratio schedules have produced relatively graded dose-response functions in individual subjects (Holloway & Gauvin, 1989; McMillan, Hardwick, & Li, 2002). Determining the conditions under which drug discrimination and generalization is quantal or graded would provide fundamental information regarding private responses to drug stimuli. In addition, studies examining whether the shape of generalization functions systematically differ across drug classes, routes of administration, time course of administration, etc., would be highly interesting. These controlling variables are not well understood and careful examination could reveal fundamental laws of interoceptive stimulus control. Moreover, if systematic differences across drug classes are found, receptor signaling systems activated by particular drug stimuli may provide important clues relevant to neural substrates of these private events.

Finally, although behavior under the control of private stimuli can often appear very complex, drug discrimination procedures could be useful in elucidating the conditions that give rise to such complexity. For example, previous studies have shown that drug discrimination performance is often robust and enduring, and this could be exploited for studying the development of complex behavioral repertoires under the control of interoceptive stimuli. In a study by McMillan, Sun, & Hardwick (1996), pigeons were first trained to discriminate pentobarbital from saline. Drugs with pharmacological effects similar to those of pentobarbital (amobarbital and diazepam) increased drug lever responding whereas other drugs (morphine and amphetamine) did not, reflecting the pharmacological selectivity of drug discrimination noted above. However, the same pigeons were subsequently trained to discriminate either morphine or amphetamine from saline. When tested later, the pentobarbital-saline discrimination was retained even after the morphine (or amphetamine)-saline discrimination was established. This study demonstrated that 1) drug stimuli continue to exert discriminative stimuli control for long periods of time after discontinuation of explicit training and despite intervening periods of training with other drugs, and 2) multiple drugs can be established as discriminative stimuli through successive training in the same subject. This type of experiment is complex and laborious, not something often found in the drug discrimination literature as it is currently employed. Nevertheless, programming an assortment of escalating multiple sequential and/or concurrent drug discriminations might be useful in understanding the establishment and maintenance of complex behavioral repertoires under the control of private stimuli.

Conclusion

The inclusion of private events within a science of behavior is a defining feature of Skinner's radical behaviorism. Recent philosophic commentary on the subject of privacy suggests that it remains a valued feature of contemporary behavior analysis. However, empirical study of privacy is not an active research domain. Drug discrimination is a powerful tool that has improved our understanding of *in vivo* pharmacology. Empirical evaluation of key parameters and variables of the standard practice and its variants would likely further enhance its value as a pharmacologic tool. Moreover, examination of this sort is directly

relevant to the study of privacy and would almost certainly provide a stimulating avenue for behavior analysts to explore private events within a controlled environment.

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Figure 1.

Idealized data representing possible outcomes in drug discrimination. The circles left of the abscissa break represent discriminative performance in a well-trained subject with near-zero response allocation on the drug lever following pre-session administration of vehicle (V) and near-exclusive allocation of responding on the drug lever following pre-session administration of the training dose (TD). The circles right of the abscissa break represents a dose-response function derived from administering doses of the training drug smaller than the training dose. The upright triangles and inverted triangles represent dose-response functions from test drugs that fully generalize to the training drug with, respectively, higher and lower potency. The squares represent a dose-response function of a test drug that partially generalizes to the training drug indicative of a partial agonist profile. The diamonds represent a dose-response function of a test drug that did not generalize to the training drug and would be considered a negative control.