

## How Will We Know a Lapse When We See One? Comment on Leri and Stewart (2002)

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The article by F. Leri and J. Stewart (2002) addresses the validity of animal models of relapse in a more sophisticated manner than does much prior research. These researchers have shown that drug self-administration can be influenced by the presence of drug contingent cues as well as by active self-administration versus passive infusion of “lapse” doses. This research also leads to additional questions about the external validity of animal relapse models. Current relapse models may lack validity because of the parameters of drug exposure, because abstinence is imposed on the organism, and because there is no motivational influence that counters resumption of drug self-administration. F. Leri and J. Stewart’s (2002) article encourages a more thorough assessment of the motivational context of relapse models.

We were asked to provide a peer commentary with respect to the article, “The Consequences of Different ‘Lapses’ on Relapse to Heroin Seeking in Rats,” by Francesco Leri and Jane Stewart (2002). It is a pleasure to provide commentary because this article was intriguing and thought provoking.

One reason that the work is thought provoking is that it raises important questions about the fundamental nature of relapse. As the authors note, relapse is not synonymous with any resumption of drug use after a period of abstinence. Rather, a modest resumption of use that is quickly curtailed (i.e., a “lapse”) does not really capture relapse in a way that reflects its clinical or theoretical significance. Given a fundamental distinction between a lapse and relapse, the authors rightly question whether there is something about the nature of the lapse, or lapse process, that influences the trajectory of future drug use. In particular, the authors ask whether a lapse-induced acceleration of drug self-administration depends on the organism’s engaging in the instrumental act of self-administration or whether a lapse increases subsequent drug self-administration because of drug effects per se (i.e., passive infusion exerts effects similar to those produced by self-administration). In addition, the authors systematically evaluate the impact of stimulus–contextual features of the lapse on animals’ subsequent self-administration behavior.

Leri and Stewart’s (2002) results showed interesting and rather robust effects of cue contingencies and control over drug delivery on self-administration behavior. For instance, the presence of contextual stimuli previously contingent

with drug infusions was associated with increased drug self-administration during both the lapse as well as the relapse sessions. However, the presence of these stimuli during the lapse exerted relatively little impact during the subsequent drug availability (i.e., the relapse). Instead, the self-administration of drug during the relapse appeared to be influenced by a prior contingency between lever pressing and drug effects during the lapse.

What are the potential messages of this work? One message is that drug exposure, per se, does not lead to as strong a resumption of drug self-administration as does drug infusion contingent with the execution of a previously drug-consequated operant. Hence, a maximal increase in the trajectory of drug self-administration may require not just that the organism is reminded of drug effects but is reminded instead of the response–drug nexus.

Another potentially important observation of this research is that an apparently effective prod to greater drug self-administration over time is not drug exposure or drug self-administration, per se, but rather drug availability and exposure following a period of deprivation. Thus, the authors note that, across self-administration sessions, initial responding for the drug increased steadily (relative to the prior session) after each period of drug abstinence that preceded the sessions. Moreover, this boost in self-administration was greatest after the prolonged period of drug deprivation imposed by the extinction procedure. This observation joins a growing body of evidence that suggests that researchers may have too blithely jettisoned deprivation as a vital explanatory element in their attempt to account for the motivation to use addictive drugs. Although substantial evidence indicates that addictive drugs can serve as positive reinforcers and impart incentive effects, too little attention has been directed at how negative and positive reinforcement processes may interact in affecting the future incentive value of the drug or how deprivation, per se, may inflate future incentive value. Thus, like other restorative or repleting responses, what is crucial is not that the organism experiences drug effects and the effects of deprivation but

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that the organism emits responses that yield drug effects in the context of deprivation (Hall, Arnold, & Myers, 2000). This comment is predicated on the notion that the animals in this research did acquire some degree of dependence during their drug exposure. This surmise is supported by previous research revealing evidence of physical dependence after modest opiate exposure (Bickel, Stitzer, Liebson, & Bigelow, 1988; Heischman, Stitzer, Bigelow, & Liebson, 1989; Martin & Eades, 1961).

Although authors have previously suggested that deprivation enhances the incentive or reinforcing value of drugs (Baker, Morse, & Sherman, 1987; Robinson & Berridge, 1993; Stewart, de Wit, & Eikelboom, 1984), this phenomenon may not have received the level of attention it deserves. Indeed, recent research suggests it is in the context of significant deprivation and withdrawal that reinforcing and incentive effects are most pronounced (Pomerleau & Pomerleau, 1992; Ying, 1998; Zinser, Fiore, Davidson, & Baker, 1999).

### Critique

Although impressed by Leri and Stewart's (2002) carefully designed study, we found ourselves asking questions about several aspects of this research. Some of these questions were narrowly methodological. For instance, one question concerned the purpose of the yoked control condition. It was hard to determine what it really controlled. This is because the yoked control condition produced a fairly high contingency between lever pressing and drug effects (as observed by the authors). Thus, although delivery of the drug was not dependent on lever pressing, it was contingent, which is perhaps of greater theoretical importance. Another concern is that in the passive heroin group (PassH), the animals spent the first 60 min of the lapse session lever pressing for saline. These animals were then given heroin infusions after the session (while they remained in the experimental chamber). This procedure may have attenuated these animals' subsequent lever pressing for heroin for two reasons not necessarily intrinsic to the concept of passive infusion. First, the 60 min of lever pressing for saline could be construed as an extra extinction trial (one more session than was given other groups that received heroin during the lapse session). In addition, the contrast of lever pressing for saline and then the infusion of heroin shortly after the lever was withdrawn could be construed as an explicit unpairing of the drug and the operant. Could these factors have been partly responsible for the low self-administration rates of PassH rats in the relapse test?

One conceptual concern is that it is unclear that a juxtaposition of direct priming models versus indirect cognitive models is the optimal way to frame this study. The cognitive model (e.g., the abstinence violation effect model) is predicated on the notion that failure to achieve or maintain a self-regulatory goal should induce negative affect, namely, blame and self-recrimination. As the authors are aware, animal models may not be optimal for exploring such mechanisms.

Thus, what the authors are really doing is not contrasting cognitive versus noncognitive models (and it is important to recognize that it is difficult to dichotomize information-neural processing into cognitive vs. noncognitive types) but instead trying to determine whether drug exposure and related variables can foster subsequent, increased self-administration. It is, of course, entirely possible that, even though drug exposure leads to subsequent increased self-administration, the lapse-relapse process, or other aspects of human addiction, those phenomena are nevertheless highly influenced by causal attributions, self-blame, negative expectancies, and so on. Thus, in some sense, the juxtaposition in the introduction of the priming model and the cognitive model is unfortunate. The data really do not speak to the relative validities of the two sorts of possible influences, and these influences need not be mutually exclusive.

Perhaps the greatest contribution of this article is that it encourages the reader to consider the external validity of animal models of the relapse process. However, this activity leads us to question several aspects of the current work as they relate to relapse among humans with addictive disorders. These questions revolve around the following issues:

One factor that reduces the match of the present experimental paradigm to the typical relapse context is that the duration of drug or self-administration was very brief in Leri and Stewart's (2002) study. Indeed, seven self-administration sessions may have been too few to foster a high level of self-administration that reflected a true addictive baseline. Also, the small number of self-administration sessions may have caused the study manipulations to "loom large" because the lapse experience was such a sizeable proportion of the rats' total drug experience.

A relapse paradigm is valid to the extent that it allows us to model psychological or physiological processes involved in the progression from initial drug resampling to previous high levels of use. We note that relapse is often characterized by a pattern of low initial use that eventually converts to full-blown use, albeit with considerable variability (e.g., Brandon, Tiffany, Obremski, & Baker, 1990). There is evidence in the Leri and Stewart (2002) research that the experimental imposition of periodic drug availability corresponding to a lapse and then relapse, does not reproduce this pattern, at least not as it is captured by a comparison of data from the self-administration phase with data from the lapse phase. For instance, during the last (seventh) self-administration session, rats self-administered about three heroin infusions and made approximately seven total responses (B-55 min data). Relevant self-administration data for the lapse session for the heroin with conditioned stimulus group were about 6 and 12 infusions. This raises the question of whether imposed drug availability and nonavailability really captures psychologically meaningful relapse processes. We may be studying less the psychology of the lapse and more the psychology of the binge. We use the term *binge* because it implies no countervailing force intrinsic to the organism that would limit drug use.

In the Leri and Stewart (2002) study, self-administration behavior was never extinguished (see Figure 2 in that

study). One typically thinks of relapse as occurring after some period in which the organism has desisted from drug seeking.

Perhaps the most significant concern with respect to animal models of relapse is that researchers have not modeled the interplay of motivational influences that occurs over the course of addictive drug use in humans, and that sets the stage for abstinence. These motivational forces must be overcome or neutralized for relapse to occur. That is, the authors never created a psychological or motivational context that produced drug abstinence.

Without the creation of countervailing motives, relapse research becomes the study of availability, that is, in the Leri and Stewart (2002) study, all that animals required in order to resume significant drug self-administration was information that drug was once more available via lever pressing. Although information on drug availability can exert potent effects in human addicts (Juliano & Brandon, 1998; Zinzer et al., 1999), we wonder whether this is indeed a crucial determinant of relapse. How many smokers trying to quit do not know that nicotine is readily available from the nearest convenience store or obliging tobacco user? Indeed, why should an organism not resume the self-administration of any appetitive commodity when it yields pleasure and produces no cost? It is unlikely that the rat has any appreciation of the ultimate costs of addiction, just as William James's "broody hen" had no prophetic inkling of the results of sitting on eggs (James, 1890/1950).

In sum, one of the defining features of relapse may be the resumption of drug use despite strong reasons not to do so, for example, punishment, or anticipated punishment, for "falling off the wagon" (see Breiner, Stritzke, & Lang, 1999). Ignoring this press for abstinence could mislead researchers in their attempt to characterize the nature of relapse precipitants. Let us assume for the sake of argument that addictive drug motivation is multifactorial (e.g., it reflects the impact of positive reinforcement, negative reinforcement, and overconfidence in estimates of control). It may be, in fact, that there is a hierarchy of motives, with some producing particularly compelling motivation. Cues and contingencies that may be efficacious signals of availability may be ineffective in the presence of strong motives against drug use. In short, we are suggesting that by ignoring the psychological features of the relapse situation, we may be casting too wide a net, capturing dross along with potent relapse precipitants.

In conclusion, it may be that researchers have not paid sufficient attention to the behavioral and psychopharmacological processes that characterize clinical phenomena such as lapses and relapses. The work of Leri and Stewart (2002) is an important step toward a more careful analysis and unpacking of these phenomena.

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