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Conditioned Stimuli's Role in Relapse: Pre-Clinical Research on Pavlovian Instrumental Transfer

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Abstract

Rationale and Objective—Pavlovian learning is central to many theories of addiction. In these theories, stimuli paired with drug ingestion become Conditioned Stimuli (CS) and subsequently elicit drug-seeking and -taking. However in most relevant studies, Pavlovian and instrumental learning are confounded. This confound may be avoided in Pavlovian-Instrumental-Transfer (PIT) procedures. In PIT, Pavlovian and instrumental learning are established separately, and then combined. In order to better understand the role of CSs in addiction, we review the relevant studies using PIT.

Findings—We identified seven articles examining PIT effects of ethanol- or cocaine-paired CSs. Under at least one condition six of these articles reported CS-elicited increases in responding previously maintained by drug. However, the only study using the optimal control condition failed to find a CS-elicited increase. Two studies examining CS specificity found the CS also increased responding maintained by a different reinforcer. Two studies examined if CSs elicit increases in actual drug-taking. Both failed to find CS-elicited increases, *i.e.*, no study shows CS-elicited increases in actual drug-taking. Further, CS-elicited increases in extinguished responding are short-lived.

Conclusions—These findings are not entirely consistent with Pavlovian learning playing a central role in addiction. However, design issues can explain most of these inconsistencies. Studies without these design issues are needed. Additionally, existing theories hypothesize drug-paired CSs increase drug-taking by increasing motivation, by eliciting conditioned responses that make drug-seeking more probable, or by a combination of these. Work distinguishing between these mechanisms would also be useful.

Keywords

Conditioned Response; Sign-Tracking; Goal-Tracking; Motivation; Alcoholism; self-administration; discriminative stimulus; conditioned reinforcement; conditioned approach; incentive salience

Introduction

Pavlovian learning is widely accepted to play an important role in relapse (see Perry et al 2014). The role of Pavlovian learning is thought to involve stimuli paired with drug ingestion (and subsequent drug effects) becoming conditioned stimuli (CS) or occasion setters. These stimuli then increase motivation for drug-taking, elicit or occasion behavior making drug-taking more probable, or both.

Various theories tend to differentially emphasize these possible actions of drug-paired CS in addiction. In some, a CS increases motivation by eliciting withdrawal-like effects (Wikler 1948), eliciting allostatic changes (Koob et al. 1989), or eliciting drug-like effects (Stewart 1984). CS-elicited drug-opposite effects may increase a drug's reinforcing effectiveness much like food-deprivation increases food's effectiveness at reinforcing behavior, *i.e.*, the CS functions as an establishing operation (Michael 1982). Alternatively, CS elicited drug-like effects may increase motivation similar to how an appetizer whets one's anticipation of the meal (Stewart et al 1984). Other theories emphasize stimulus-induced behavior, which increases the probability of drug-taking or seeking (Tomie 1995). A CS, such as a martini glass, elicits approach. Coming nearer to the glass because of its proximity to the gin bottle (itself a CS) increases the likelihood gin is mixed with vermouth, resulting in a martini. The presence of the martini increases the probability of its ingestion. Lastly, increases in motivation may work hand-in-hand with changes in behavior to cause relapse (Robinson & Berridge 1993). Understanding the roles of Pavlovian learning in relapse would be facilitated if we could isolate the role of Pavlovian learning from those of other learning processes.

Surprisingly, isolating the role of Pavlovian learning is not possible in the majority of studies showing increases in drug-taking or -seeking following presentation of drug-paired stimuli. Many studies show discriminative stimuli that were not present during extinction increase or reinstate drug-seeking (see Crombag et al 2008). This is consistent with other studies showing that responding in the presence of a discriminative stimulus is higher than its absence (*e.g.*, Lamb & Jarbe 2001), that discriminative stimuli can control differential responding for ethanol and food (*e.g.*, Ginsburg et al 2005), and that the presence of two separately trained discriminative stimuli can increase responding for drug beyond that seen with either stimulus alone (Panlilio et al 1996; Panlilio et al 2000). As these discriminative stimuli are paired with drug administration, they likely function as CSs. However, this temporal relationship was obtained through instrumental conditioning, and the two types of learning cannot be easily disentangled (but see, Weiss & Schindler 1987). Further, a stimulus's role as a discriminative stimulus cannot be reduced to its function as a CS. Mackintosh (1983, pp.100–112), in his still classic discussion of this, points out three types of findings that show discriminative stimuli are not simply Pavlovian CSs: (1) a stimulus can

be established as a discriminative stimulus even when it predicts no change in the rate of delivery of the Unconditioned Stimulus (US), *i.e.*, the US is delivered contingently in the stimulus's presence and non-contingently in its absence, a condition that would prevent the establishment of the stimulus as a CS (Colwill & Rescorla 1988); (2) if instrumental responding produces a CS paired with the delivery of a US, then peripheral Conditioned Responses (CR) follow execution of the instrumental response rather than onset of the discriminative stimulus (Ellison & Konorski 1964); and (3) a discriminative stimulus will not block the establishment of a different stimulus as a CS, nor will a CS block the establishment of another stimulus as a discriminative stimulus (Holman & Mackintosh 1981). Further, a stimulus established as a discriminative stimulus for one response with a particular consequence will show greater facilitation of another response for the same consequence (when this behavior is in extinction) than a stimulus established as a CS for the same consequence (Rescorla 1994). A result that would seem to indicate a greater involvement of instrumental learning in the roles that CSs are thought to play in addiction.

Second-order schedules offer another way in which the influence of drug-paired stimuli on drug-taking and -seeking might be studied, and studies of second-order schedules have contributed importantly to our understanding of the roles of drug-paired stimuli in addiction (Goldberg et al 1990; Schindler et al 2002). However, these stimuli are part of the contingent relationship resulting in drug-delivery; thus, instrumental learning can play a crucial role in any effect these have on drug-taking or -seeking. Similarly, extinguished drug seeking may be reinstated by presentation of a stimulus paired with contingent drug delivery (*e.g.*, de Wit & Stewart, 1981). Again however, this could result from either instrumental learning, Pavlovian learning, or both. Finally, studies examining the conditioned reinforcing effects of stimuli signaling the availability of response-contingent drug have greatly improved our understanding of addiction (Shahan 2002; Woods & Winger 2002), but in these studies, as well, the roles of instrumental and Pavlovian learning are hard to separate. Thus, while these studies clearly show that drug-paired stimuli can facilitate drug-taking and -seeking, these studies do not separate out the contributions of instrumental and Pavlovian learning, and thus, do not allow us to assess the independent role of Pavlovian learning in relapse.

However, procedures do exist for assessing the effects of Pavlovian learning on instrumental responding. For instance, Davis & Smith (1976) paired a stimulus with drug delivery and showed that making stimulus-presentation response-contingent maintained responding (see also Leri et al 2009). Thus, drug-paired stimuli can at least temporarily maintain behavior as a result of Pavlovian learning. This finding compliments studies showing that drug-paired stimuli can elicit approach (Cunningham & Patel 2007; Uslaner et al 2006; Peters & de Vries 2014; Srey et al 2015; but see Kearns & Weiss 2004). Both elicited approach and conditioned reinforcement could play important roles in relapse. Searching the environment might be reinforced by a drug-paired stimulus. Approaching this stimulus often brings one closer to materials needed for drug use; and this closer proximity will increase the probability of drug use. Such an account of the role of CSs in relapse is more consistent with some theories (Tomie 1995) than others (Wikler 1948). However, these findings do not directly address whether Pavlovian learning can result in increased drug-taking or -seeking and thus, promote relapse. Further, these findings can be interpreted as supporting either

increased motivation or CS-elicited/occasioned behavior resulting in an increased probability of drug-taking or seeking.

A procedure that may help address these issues is Pavlovian-Instrumental-Transfer (PIT). With PIT, the CS-US relationship is trained separately from the instrumental relationship maintained by the US (Estes 1943). Subsequently, the effect of the CS upon instrumental responding is assessed. Below, we review the results from pre-clinical studies examining PIT using drug-maintained behavior.

CS-elicited Increases in Responding in Comparison to a Control Condition

We were able to identify seven papers (see Table 1) that examined PIT on behavior that had previously been maintained by either ethanol (Krank 2003; Glasner et al 2005; Corbit & Janak 2007; Krank, et al 2008; Milton et al 2012) or cocaine (Kruzich et al. 2001; LeBlanc et al 2012). Six of these seven papers showed that at least under some conditions presentation of the ethanol- or cocaine-paired CS could increase instrumental behavior that had been previously reinforced by ethanol or cocaine (Krank 2003; Glasner et al 2005; Corbit & Janak 2007; Krank et al 2008; LeBlanc et al 2012; Milton et al 2012), while one paper with cocaine did not (Kruzich et al 2001).

The increases that were seen in the six papers were in comparison to either responding by an explicitly unpaired stimulus group (Krank 2003; Krank et al 2008), responding by the same animals to a stimulus that was explicitly unpaired and had been presented a similar number of times as the CS (Corbit & Janak 2007) or had been presented on substantially fewer occasions (LeBlanc et al 2012; Milton et al 2012) and/or to responding in the period between CS presentations (Krank 2003; Glasner et al 2005; Corbit & Janak 2007; Krank, et al 2008, LeBlanc et al 2012; Milton et al 2012).

The one study with cocaine that did not see an increase in responding following CS presentation used a compound light-tone CS, and compared responding during the CS to responding during light-tone presentations by a Truly-Random-Control Group (Kruzich et al 2001). In this Control Group, each element of the compound and cocaine had been delivered according to independent random time schedules. A Truly-Random-Control procedure is the proper control procedure for examining the effects of a CS, as this procedure controls for other types of non-associative conditioning that might occur and avoids a problem seen with explicitly unpaired stimuli, *i.e.*, explicitly unpaired stimuli can come to predict non-delivery of the US (Rescorla 1967). Thus, it is problematic that the only study using a Truly-Random-Control procedure is the sole study failing to demonstrate an increase in responding following CS presentation.

Several factors mitigate this negative finding. First, the Truly-Random-Control procedure used by Kruzich et al presented each element of the compound stimulus according to independent random time schedules. Thus, the stimulus compound was relatively novel in this group, which casts some doubt on the appropriateness of the comparison. Second, the CS was relatively short, 5-seconds. Shorter CSs are more likely to elicit behavior competing directly with responding, and would thus be less likely to increase responding. Finally,

Kruzich et al used relatively long experimental sessions (3-hour) with CS presentations occurring every 10-minutes. As discussed later, the effectiveness of a CS at increasing responding in PIT declines rapidly. In fact, Kruzich et al found that responding following the CS declined in both the experimental and control groups from the first to the third hour of the session; and while an ANOVA indicated no differences in responding across groups (which included other experimental groups as well) across time, examination of their Figure 3 indicates that a difference between the Experimental and Truly Random Control groups may have existed at the first time-points. Clearly, studies with ethanol or cocaine (or some other drug) comparing CS effects obtained in a PIT procedure to those of a Truly-Random-Control procedure would fill an important knowledge gap about the role of drug-paired CSs in relapse.

Another difference between Kruzich et al (2001) and the studies with ethanol was the absence of a consummatory response. In Kruzich et al, cocaine was delivered intravenously. Thus, no consummatory response was required for the rat's behavior to be reinforced by cocaine. With ethanol, however, the rat must approach and then drink the ethanol. This consummatory response is part of the sequence of instrumental behaviors and also a CR elicited by the ethanol-paired CS. Thus, the ethanol-paired CS may elicit this CR, which then sets the occasion for responding. It is notable that the LeBlanc et al (2012) study with cocaine, which showed increases in responding when the CS was presented, used a chain schedule. Under the chain schedule, responses in the first 'seeking' component were reinforced by insertion of a lever on which responses were reinforced by cocaine delivery. Thus, this chain schedule consisted of a 'cocaine-seeking' component followed by a 'cocaine-taking' component. While it is tempting to speculate that this 'taking' component served the same role as the consummatory response in the ethanol studies, one should note that both levers were absent during Pavlovian conditioning. So, it would not be possible for 'taking' responses to occur during the CS-US pairings (as an aside, it is interesting to note that the PIT effect in the Le Blanc et al was most clear for responding on the 'taking' lever and that both levers were present during testing; Further, in their initial testing LeBlanc et al did not find a PIT effect, which was observed only after further extinction and combining groups).

In summary, while all but one study showed increases in responding for ethanol or cocaine following presentation of an ethanol- or cocaine-paired CS, these studies all used relatively weak control conditions. The one study using a stronger control condition did not show increases. This study, however, had methodological weaknesses that reduce this concern. Studies of PIT with ethanol or drugs using a Truly Random Control condition without these concerns would be an important addition to the literature.

Specificity of CS-elicited Increases in Responding

In PIT, a CS can produce either a specific effect, increasing only behavior for which the US also serves as a consequence, or it can increase behavior maintained by a variety of different reinforcers. Two studies have examined the specificity of drug-paired CSs in PIT procedures (Glasner et al. 2005; Corbit & Janak 2007). Both Glasner et al and Corbit & Janak report that an ethanol-paired CS increased responding that had been reinforced by ethanol and

responding on a different lever that had previously been reinforced by another reinforcer. These results are potentially problematic for theories postulating a role for Pavlovian learning in addiction, as these theories implicitly assume specific increases in drug-seeking and -taking. However, aspects of the procedures used in both studies may have made non-specific increases more likely.

Glasner et al trained rats to respond for either ethanol plus saccharin or polycose plus quinine in separate sessions. During training, the other lever for the other reinforcer was absent. Following this (again in separate sessions), they paired distinct CSs with either polycose or ethanol delivery. Subsequently, in a test session, they randomly presented the two CSs with both levers present and responding in extinction; and found that responding on both levers increased during presentation of either CS. However, polycose and ethanol were delivered using the same dipper mechanism and only one lever was ever present during the training, i.e, there was no training that arranged for the rats to discriminate between levers in order to earn ethanol or polycose; and thus the rats were not required to learn those relationships. Indeed, it is not clear that the CSs emerged from training as specific CSs for particular USs. Thus, based on what was trained, the absence of a specific effect might be expected.

The procedures used by Corbit & Janak were similar except that they conducted their test sessions with only one lever present, and CS-US pairings for both USs (ethanol and sucrose) occurred in the same session: Note, however, that ethanol and sucrose were delivered into the same magazine. Thus, again the particular procedure used may have reduced the likelihood of seeing specific increases in responding. Arguing against this criticism is Experiment 3 by Corbit & Janak (2007) in which they used the same training procedures, but instead of ethanol and sucrose, they used polycose and sucrose. In this experiment, they saw greater specificity (though one should note that the sucrose CS similarly increased responding on the sucrose and polycose levers). Further experimentation is needed to resolve the issue of specificity, as drug- or ethanol-paired CS elicited increases in behavior that are specific to drug- or ethanol-seeking is central to most theories of addiction asserting a role for Pavlovian learning.

CS-elicited Increases in Actual Drug Consumption

Another central tenet of these theories is that CS facilitation of drug- or ethanol-seeking results in an increase in drug- or ethanol-consumption. For instance, by definition relapse cannot happen unless drug is consumed. Further, it would be hard to conceive of an important role for drug-paired CSs in addiction, if at least under some conditions, a drug-paired CS could not increase drug-consumption beyond the level seen in its absence. The experiments discussed so far all involved behavior that was in extinction, that is responding in these experiments no longer resulted in cocaine or ethanol delivery, which is typical of studies of PIT. Two of the studies reviewed above also examined CS-effects on either ethanol- (Krank 2003) or cocaine-reinforced responding (LeBlanc et al 2012). In neither of these studies did the CS elicit an increase in responding. One possibility is a ceiling effect, *i.e.*, when drug is available, behavior is at its maximum level. Ginsburg & Lamb (2013a,b) argued that suppressing ethanol-maintained behavior through the reinforcement of

alternative behavior is a better way to study relapse and recovery; and a way that could conceivably prevent such ceiling effects. Similarly, Panlillo et al (2003) argued that suppressing drug self-administration by punishing responding for drug provides is a more valid model for studying relapse to drug-taking. Arguing against ceiling effects, however, are findings by Panlillo et al (2000), who found compounding two discriminative stimuli signaling heroin availability increased responding for heroin above the levels seen with either stimuli alone.

However, other possible explanations exist for the negative findings of Krank (2003) and LeBlanc et al (2012). In Krank's study, testing of the ethanol-paired CS on ethanol-reinforced responding occurred following the testing of this CS on responding for ethanol that was in extinction. As discussed later, CS-elicited increases in responding appear to be short-lived, thus, this previous testing of the CS in extinction likely reduced the subsequent effectiveness of the CS.

LeBlanc et al's Experiment 1 examined the effects of a cocaine-paired CS on responding in two groups: one that was in extinction and the other in which responding produced cocaine. The CS failed to produce robust increases in responding in either group. Only in a subsequent experiment in which both groups were combined and tested in extinction and the CS-US relationship had undergone partial extinction, was a reliable increase in responding seen following presentation of the cocaine-paired CS. LeBlanc et al hypothesize that this was because behaviors that competed with responding were elicited by the cocaine-paired CS, and these competing responses were reduced by partial extinction of the CS-US relationship; and thus, this reduction in competing behaviors made the observation of increases in cocaine-maintained responding possible.

In summary, in both Krank and LeBlanc et al, the failure to see increases in ethanol- or cocaine-maintained responding by an ethanol- or cocaine-paired CS may have been unrelated to whether behavior was reinforced by ethanol or cocaine instead of being in extinction. Clearly, given the importance of CS-elicited increases in drug consumption to theories of addiction invoking Pavlovian learning, studies explicitly designed to strongly test this issue are needed.

Role of Conditioned Responses in Changes in Responding

LeBlanc et al (2012) hypothesized that CS-elicited competing behaviors may interfere with CS-elicited increases in responding. Krank (2003) provides some evidence that this could be the case. Krank trained two cue lights as CSs: One that was located over the response lever and one that was located away from the lever. When the cue light near the lever was lit, responding increased. When the cue light away from the lever was lit, responding decreased (Experiment 1) or was unaffected (Experiment 2). Krank hypothesized that this was the result of the conditioned approach toward the cue light (or sign-tracking) that he observed in response to the cue lights being lit. Thus, if the CS is located near the response lever, this approach brings the rat nearer to the lever and increases the probability of a response. However, if the CS is located away from the lever, this approach takes the rat further from the lever and decreases the probability of a response. A subsequent study by Krank et al

(2008) used a concurrent schedule in which responding was reinforced with ethanol on two different levers and the cue lights above each lever were paired with ethanol delivery using a PIT procedure. Lighting each cue light elicited approach towards that cue light, entry into the magazine where ethanol was delivered, and contact with the lever. Tests of the effects of the CS on responding that was in extinction showed that lighting a cue light increased responding on the lever located near it, but not on the lever away from that cue light, compared to responding seen in an unpaired control group. These findings by Krank and Krank et al indicate that an ethanol- or drug-paired CS *may elicit behaviors* that can increase the probability of responding that had previously been maintained by ethanol or drug or may decrease the probability of this responding depending on the CR elicited and its relationship to the response requirement for drug or ethanol delivery. This would be consistent with theories of the role of Pavlovian learning in addiction that emphasize the importance of CS-elicited approach or sign-tracking (e.g., Tomie 1995; Flagel et al 2009).

Sign-tracking interpretations of PIT seem reasonable when the CS is fixed in space; however, they may not be as applicable when the CS is a diffuse stimulus, such as an auditory cue, as in the remaining four studies (Glasner et al 2005; Corbit & Janak 2007; LeBlanc et al 2012; Milton et al 2012), which used a 2-minute tone or clicker, as compared to the 10-second localized visual CS used by Krank or Krank et al (Krank 2003; Krank et al 2008). Compared to a brief visual stimulus located near the response lever, these longer more diffuse auditory CSs should elicit less approach that could contribute to increased responding. Still, these diffuse CSs increase responding.

This does not mean, however, that the CS-elicited increases in responding observed in these studies using diffuse auditory CSs necessarily results from CS-elicited motivational changes. Krank (Krank 2003; Krank et al 2008) noted that the ethanol-paired CS in his experiments, not only elicited approach towards the response lever, but also elicited approach towards the magazine into which the ethanol was delivered. This magazine entry would be frequently followed by lever-pressing during instrumental conditioning. Thus, magazine entry likely comes to set the occasion for (serve as a discriminative stimulus for) lever pressing; and thus, this elicited behavior may result in increases in lever-pressing during ethanol-paired CS presentations. This argument of goal-tracking serving as an occasion setter for instrumental responding is more difficult to make in the study by LeBlanc et al (2012) using intravenous cocaine, as the cocaine self-administration procedure has no obvious response that typically precedes further responding for drug that occurs both during instrumental responding and Pavlovian conditioning (see earlier discussion), which could, thus, serve as an occasion setter for further instrumental responding.

Even in this case, however, non-motivational explanations may exist. Drug-paired CSs frequently come to elicit drug-like CR (Stewart et al 1984). These drug-like CRs may result in increased responding, as administration of the drug that had previously maintained responding increases self-administration that is currently in extinction (de Wit & Stewart 1981), an effect that may be explained by drug injections frequently preceding responding for drug (Slikker et al 1984). Thus, the existing literature on drug- or ethanol-paired CS-elicited increases in responding are wholly consistent with these increases resulting from behavior elicited by the CS making responding more likely, and at least partly consistent

with this increase resulting from CS-elicited increases in motivation to consume ethanol or drug.

Extinction of CS-elicited Increases in Responding

Finally, we consider the longevity of the facilitative effects of drug-paired CSs on instrumental responding. CS-elicited increases in responding for drug or ethanol appear to extinguish rapidly. For instance Milton et al (2012) observed that the first ethanol-paired CS presentation in a test session produced robust increases in responding, but that this increase in responding disappeared over the subsequent three CS presentations. This rapid decline in the effectiveness of ethanol- or drug-paired CSs at eliciting ethanol- or drug-seeking behavior would seem at odds with the postulated roles of such stimuli in relapse: however, several factors argue against this conclusion. First, most relapse occurs shortly after the initiation of abstinence and before much opportunity for extinction of the CS-US pairing to occur. Second, within-session extinction would likely not fully carry-over to subsequent test-sessions. Therefore, between-session extinction is likely more delayed. Thirdly, extinction is context-dependent (see Todd et al 2014), and while in experimental settings context is generally constant, for people in recovery context is often varied and constantly changing. This would be expected to further slow extinction. Finally, CS-elicited increases in drug-seeking are likely to be reinforced by drug-consumption in the real world; thus, further strengthening the CS-US relationship. Additionally, this first re-occurrence of reinforced drug-seeking, this lapse, is reinforced, *i.e.*, the future probability of drug-seeking is increased. Likely this future drug-seeking would also be reinforced leading to yet more drug seeking that is reinforced and thus, to a relapse. Therefore, it may be when drug-seeking is reinforced, a transient increase in the probability of drug-seeking by a drug-paired CS is sufficient to cause relapse.

Recapitulation

These studies provide clear evidence that CSs can under certain circumstances increase responding that had been maintained by ethanol or cocaine. However, there are gaps in our knowledge limiting the extent to which the available evidence can be used to support most theories that evoke Pavlovian learning in the addictive process. Additionally, as implied during the review of these studies, the potential role of CSs in addiction may not need to invoke CS-elicited changes in motivation to explain CS-elicited changes in drug-seeking (if these occur). Such an explanation may appear to ignore many important aspects of addiction. However, such an analysis may also promote a better scientific analysis of the causal role of CSs in addiction, the biologic basis of these effects, and may also result in more effective means of promoting recovery.

Knowledge Gaps

The studies reviewed provide data indicating that cocaine- or ethanol-paired CSs may increase responding that had been maintained by ethanol or cocaine; and thus, provide evidence for a role of drug-paired CSs in relapse. However, there are clear knowledge gaps limiting our confidence in this notion and theories employing it. First, none of the studies

demonstrating a drug- or ethanol-paired CS elicited increases in responding compared these CS-effects to those obtained using a Truly Random Control. Thus, our ability to attribute observed CS-elicited increases in responding for ethanol or drug to an association between the CS and ethanol or drug is limited. The ability to assert this is central to theories invoking a role for Pavlovian learning in addiction. Second, no actual CS-elicited increases in ethanol or drug intake have been observed. This too is central to most theories invoking a role for Pavlovian learning in drug and alcohol addiction. However, CSs could cause a relapse to drug-taking by increasing the probability of drug-seeking that once reinforced results in further drug-taking, *i.e.*, relapse. Perhaps the reason that such increases in drug-taking have not been observed following presentation of a drug-paired CS relates to either examining CS-effects on behavior in which responding is in extinction and no increases in drug-taking can be seen, or studying the effects of the drug-paired CS on responding that is not suppressed. This possibility argues for studying the effects of drug-paired CSs under conditions in which responding is suppressed, but increases in responding results in increases in drug-taking (Panlillo et al 2003; Ginsburg & Lamb 2013a,b). Thirdly, the specificity of ethanol-paired CS increases in responding for ethanol has been questioned. Again, this is central to theories invoking a role for Pavlovian learning in drug or alcohol addiction. Finally, the sign-tracking and goal-tracking elicited by the ethanol- or drug-paired CS or the drug-like effects elicited by such a CS may be sufficient to account for CS-elicited increases in responding for drug: explanations that would be more consistent with some, than other theories of the role of Pavlovian learning in drug and alcohol addiction.

An Analysis based on Observed Elicited Behaviors

Drug- or ethanol-paired CSs elicit a variety of CRs. Many of these CRs might be expected, at least under certain circumstances, to increase drug- or ethanol-seeking and consumption. Many, perhaps all, of the facilitating effects on drug- or ethanol-seeking and consumption of drug- or ethanol-paired CSs can be explained by the behaviors elicited by these CSs without the need to invoke CS-elicited increases in motivation. In the following paragraphs, an outline of such an analysis is provided.

Drug- or ethanol-paired CSs will elicit a variety of drug- or ethanol-like CRs (see Eikelboom & Stewart 1982 for a discussion of when this will and will not be the case). Thus, we would expect the CRs elicited by the CS to mimic the effects of drug or ethanol administration. Administering drug or ethanol before the session increases responding previously reinforced by drug or ethanol delivery, but that is now in extinction (de Wit & Stewart 1981). Slikker et al (1984) have argued that these increases in responding result from drug-administration setting the occasion for responding, as previously all responding except that before the first drug delivery of the experimental session had been preceded by delivery of at least one drug-injection. Thus, one way a drug- or ethanol-paired CS can increase responding that had previously been maintained by drug- or ethanol-delivery is by producing drug- or ethanol-like CRs.

When drug or ethanol delivery requires a consummatory response (such as is the case with oral ethanol or drug self-administration), the drug- or ethanol-paired CS will set the occasion for the animal to approach the location where the drug or ethanol will be delivered. In most

cases, entry and exit from this location is followed by further responding for drug or ethanol. This history of entering and exiting from the location of drug or ethanol delivery being followed by further responding for drug or ethanol leads to this behavior setting the occasion for (serving as a discriminative stimulus for) further responding for drug or ethanol. Thus, if presentation of the drug- or ethanol- CS results in entry and exit from the location where drug or ethanol is delivered, this behavior occasioned by the CS will itself occasion further responding for drug or ethanol. Krank (2003) and Krank et al (2008) have noted that presentation of an ethanol-paired CS does indeed result in entry into the location of ethanol delivery. Thus, another way drug- or ethanol-paired CSs can increase responding is by producing goal-tracking.

One last way that a drug- or ethanol-paired CS can increase responding that previously had been maintained by drug or ethanol delivery is by eliciting sign-tracking. If the CS is a localized stimulus, then presentation of a drug- or ethanol-paired CS will often elicit approach towards the stimulus (Krank 2003; Urslander et al 2006; Cunningham & Patel 2007; Krank et al 2008; Srey et al 2015). When such stimuli are located near the lever on which responding for drug or ethanol would occur, the CR of moving towards the CS brings the animal nearer to the lever and thus, increases the probability of the animal pressing the lever. Thus, drug- or ethanol-paired CSs may increase responding that previously had been maintained by drug or ethanol delivery by sign-tracking, if the CS is located near the response-location, goal-tracking and by producing drug- or ethanol-like effects.

The behaviors resulting from CS presentation are sufficient to explain the increases in previously reinforced responding seen following CS presentations. Behaviors such as goal-tracking or sign-tracking could result from CS-elicited changes in motivation, but it is not necessary to evoke changes in motivation to account for either these behaviors or the increases in responding that may be seen following these behaviors. Similarly, CS-elicited drug- or ethanol-like CRs might increase motivation for drug or ethanol, but it is not necessary to evoke such changes to account for increases in responding. Rather, these CRs sharing discriminative stimulus effects with the self-administered drug would be sufficient. Thus, evoking CS-elicited increases in motivation does not appear necessary to explain the increases in previously reinforced responding seen following presentation of a drug- or ethanol-paired CS.

Limitations of Explaining Increases in Drug Taking in Terms of Observable Elicited Behavior

Explanations of increased ethanol- or drug-seeking behavior following presentation of an ethanol- or drug-paired CS in terms of some change in the motivation of the organism elicited by the CS have at least two potential advantages over explanations evoking only changes in observable behavior. First, invoking changes in motivation may point to biologic changes responsible for these increases, and understanding the biologic mechanisms would have many subsequent advantages, such as in developing new medications to treat addiction, and improving our understanding of the biologic basis of learning. Second such explanations

may also have heuristic value, increasing our ability to understand the phenomenon and to make predictions.

We feel that giving too much weight to the first of these benefits, *e.g.*, that attributing changes in responding to changes in motivation will aid us in searching for biologic mechanisms, is a mistake. The search for biologic mechanisms and the specification of the particular behaviors involved in CS-elicited increases in drug-seeking, we feel go hand in hand (see Berridge & Robinson 2003 for a related discussion). The recent work of Flagel et al (2011) in which they examine the role of dopamine in approach elicited by a food-paired CS provides a nice example. The explanation of behavior at a biologic level requires first specifying the behavior you are investigating and is facilitated by understanding the determinants of this behavior, as this understanding of the behavior will allow you to manipulate it, and thus examine the relationship between it and its purported biologic mechanism.

Theories of CS-elicited increases in drug-seeking sometimes explain these increases by evoking increased motivation for drug. Evoking this increased desire as an explanation has great heuristic value. We know what to expect from an increase in motivation: greater more vigorous drug-seeking, greater drug-consumption, and so on.

Advantages of evoking CS-elicited CRs

When this heuristic leads to accurate predictions, we feel we have explained why the behavior we observed occurs. While explaining the resulting behavior in terms of the CS-elicited CR, still leaves us looking for an explanation for the CR. However, such a description of CS-elicited changes in drug or ethanol-seeking and consumption has some advantages. The CS-elicited CR has the potential of being more specific, more measurable and more observable than CS-elicited changes in motivation. Changes in motivation mean different things to different people. If we take it to mean increases in responding, then we really have only described the result in terms of the result. There are other definitions of motivation. However most are problematic. They either define motivation in terms of the phenomenon they wish to explain or involve processes that are not measurable. For instance, Robinson & Berridge speak about incentive salience in terms of its attributes: conditioned approach, conditioned reinforcement, and PIT (Berridge & Robinson 2003). When used in this sense motivation is, of course, not used to explain PIT. Rather, PIT is an attribute of motivation.

It may be useful to examine the effect of recasting a theory in terms of specific behavior, rather than through the use of hypothetical constructs such as motivation. For instance, in allostatic theory (Koob et al. 1989), CSs through an opponent process elicit drug-opposite CRs that increase drug-taking. This is described as occurring as a result of a changing hedonic set-point, and the change in hedonic set-point is hypothesized to increase motivation. This increased motivation is typically demonstrated by an increased progressive-ratio breakpoint for drug-maintained responding. Thus, a specific type of CR, drug opposite effects, results in a specific behavior, increased breakpoints. A change in hedonic set-point is used to explain the increase in breakpoint. However, the explanatory power and utility of the

theory does not depend upon this hypothetical construct. Simply focusing on these two specific types of behaviors (drug-opposite CRs and increased breakpoints) might facilitate our understanding of important phenomena that are predicted by allostatic theory *e.g.*, escalation (see Ahmed & Koob 1998). Breakpoint can increase through either increases in unconstrained demand (the amount consumed when no work is required for consumption) or decreases in elasticity (the amount consumption decreases with an increase in the work requirement) or both (Lamb & Daws 2013). Increases in unconstrained demand results in an escalation in drug use at a given price. Crucially, CS-elicited drug opposite CRs offer a potential explanation for increases in unconstrained demand. Unconstrained demand may be limited by a variety of factors, (1) drug induced impairment preventing further drug-intake (Spealman & Kelleher 1979; Herling & Woods 1980), (2) drug-induced aversive effects (Cunningham & Niehus 1989; Shabani et al 2011), or (3) habituation (McSweeney et al 2005; Murphy et al 2006). CS-elicited drug opposite CRs might well be expected to increase the level of drug that could be consumed before encountering drug-induced impairment, aversive effects or habituation: Possibilities that can be experimentally investigated. Thus, focusing on the behaviors specified within a theory provides a way to study the mechanisms that may be responsible for the escalation of drug intake in addiction.

There are additional advantages of focusing on the specific CRs elicited by the drug-paired CS. In particular, as we learn how the form of the CR changes with the parameters of its conditioning, we should be able to predict how the effects of the CS on responding should change. For instance in Krank (2003), there is no reason to believe that the CS located near the lever location should increase motivation for ethanol and the CS away from the lever location should decrease motivation for ethanol, but there is every reason that both CSs should elicit approach towards that light; and further to believe that greater proximity of the light to the lever would increase the probability of lever pressing. Similarly, the non-specific effects observed by Glasner et al (2005) and Corbit & Janak (2007) might result from a CR like magazine approach being followed by pressing either lever, given the rat's training history. Thus, by knowing the form of the CR, we may be able to more accurately predict the effects of the CS on ethanol- or drug-seeking, than by simply evoking CS-elicited increases in motivation.

Conclusion

Pavlovian learning plays a central role in many theories of addiction, particularly with regard to relapse. In broad terms, encountering drug-paired CSs are hypothesized to precipitate relapse, often, though not always, by increasing motivation to take drugs. Presumably, if a drug-paired CS increases motivation to take drugs, then a drug-paired CS should increase drug consumption. Yet there is no evidence that this can occur (Krank 2003; LeBlanc et al 2012). This lack of evidence may be because drug-paired CSs do not increase motivation to take drugs or because the appropriate experiments have not been conducted. Further, the one experiment designed to test whether increases in drug-seeking seen following presentation of a drug-paired stimulus resulted from associative learning did not find increased drug-seeking (Kruzich et al 2001). Again, this may be because drug-paired stimuli do not increase drug-seeking through Pavlovian learning or because the appropriate experiments have not been conducted. Finally, the increases in responding seen following presentation of a drug-paired

stimulus may not be specific to drug-seeking (Glasner et al 2005; Corbit & Janak 2007). This may be because drug-paired stimuli increase the frequency of many different behaviors, or because the appropriate experiments to show specific effects have not yet been conducted. Certainly, drug-paired stimuli play a role in addiction. Discriminative stimuli can reinstate drug-seeking that was extinguished in their absence (see Crombag et al 2008) and combining two discriminative stimuli increase drug-seeking (Panlilio et al 1996; Panlilio et al 2000) and drug-taking (Panlilio et al 2000) above levels seen with either stimulus alone.

So, the question is not whether drug-paired stimuli play a role in addiction, but whether Pavlovian learning plays a role in addiction. Even if drug-paired CSs do not increase motivation to take drugs, drug-paired CSs may produce effects that increase relapse risk or further addiction in other ways. Presentation of drug-paired CSs can reinforce the behavior that precedes their presentation. Thus, drug-paired CSs reinforce behavior that brings one into contact with the CS. Drug-paired CSs also elicit approach towards the CS. Thus, drug-paired CSs reinforce attending to the CS and elicit approach towards the CS. This approach towards the drug-paired CS will often increase one's proximity to the materials needed to consume the drug. Further, in the presence of this CS drug-seeking has likely been reinforced by drug-consumption (*i.e.*, often the CS is also a discriminative stimulus). This proximity and this discriminative function of the stimulus would be expected to increase the probability of drug-taking. Therefore, it seems clear that Pavlovian learning will play a role in the development of and the relapse to addiction. The question is what is this role? Is it simply like that outlined above increasing the probability that the occasion is set for drug-taking? Or does the drug-paired CS additionally act as an establishing operation to increase the amount of drug consumed or the resistance of drug-maintained behavior to change as the costs of consumption are increased?

These are not trivial questions at any level. Still, these questions are important not only at a theoretical level, but also at a practical level. Our theoretical perspective guides us in how we approach a problem. Thus, focusing our work and our interpretation of our work. For instance, drug self-administration research began mostly with researchers steeped in the operant tradition and this led them to look first at addiction as an example of reinforced behavior (*e.g.*, Schuster 1976; Griffiths et al 1980), and then more recently as an example of choice behavior (*e.g.*, Heyman 2009; Vuchinich & Tucker 1988; Lamb et al submitted). Only rarely did these researchers investigate questions related to the role of Pavlovian stimuli in addiction with rigor (*e.g.*, Goldberg et al 1969; Goldberg et al 1976; Goldberg et al 1979). However, slowly, but with increasing speed, researchers steeped in associative learning traditions have begun to study addiction (*e.g.*, de Wit & Stewart 1981; Cunningham & Niehus 1989; Panlilio et al 1996; Kearns & Weiss 2004; Glasner et al 2005; Corbit & Janak 2007). Their work has made it possible to more clearly understand the roles of associative learning in addiction. Interestingly, researchers from the associative learning tradition have begun to propose theories of addiction that diverge from the accounts discussed within this manuscript. For instance, Hogarth et al (2013) theorize that repeated drug ingestion facilitates the transition from the control of behavior by response-outcome and stimulus-outcome-response relationships in which both the sensory and affective properties of the outcomes play a crucial role *to the control of behavior by stimulus-response and [stimulus-outcome]-response relationships* in which the affective (but not the sensory)

properties of the outcome play a crucial role: A change in control from goal-directed to habitual behavior. They posit that this transition of the behavior from goal-directed to habitual results in a narrower, less flexible behavioral repertoire that is dominated by drug use.

They point out that this viewpoint leads to emphasizing the use of therapeutic approaches that reinforce alternative behaviors and enhance the representations of future consequences, as opposed to treatments emphasizing extinction or challenging expectations. Additionally, the neural systems that mediate specific transfer (stimulus-outcome-response) and general transfer ([stimulus-outcome]-response) differ (*e.g.*, Corbit & Balleine 2005, 2011) and the neural systems that mediate response-outcome relationships and stimulus-response relationships differ (Killcross & Coutureau 2003), which suggests specific biologic approaches to treatment. Similarly, a viewpoint that emphasizes the behaviors elicited by drug-paired CSs and their role in the discriminative control of behavior may suggest other therapeutic approaches. The same is true for viewpoints suggesting that drug-paired CSs function as establishing operations increasing motivation. Because these differing viewpoints suggest differing therapeutic approaches, future experiments need to be designed not only to address the knowledge gaps outlined, but also to examine the behavioral and neurobiological mechanisms by which learning results in addictive behavior and relapse. Such experiments will benefit from the use of experimental models using procedures other than extinction to suppress drug use (*e.g.*, Panlilio et al 2003; Ginsburg & Lamb 2013a,b), as these other models appear to be more relevant to the processes operating in relapse and recovery (see Lamb et al submitted).

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Table 1

Characteristics of Reviewed Studies

Study	Drug	schedule ^A (session time)	training order ^B	CS	CS training details ^C
Kruzich et al	0.25 mg cocaine	FR1 (3h)	intermixed 14-O/2-P	5-s Tone & Light	CS presentation #-average cocaine injections earned evenly spaced
Krank					
exp 1	0.1 ml 10%(v/v) ethanol + 0.1% (w/v) saccharin	VI 10-s (0.5h)	10-O then 10-P	10-s cue light	average ITI=100-s, US=0.2ml
exp 2	0.1 ml 10%(v/v) ethanol + 0.1% (w/v) saccharin		10-O then 8-P	10-s cue light	average ITI=100-s, US=0.2ml
Glasner et al					
	0.1 ml 10% (w/v) ethanol+0.15% saccharin	RR5 (30.5h)	O then 7-P	120-s tone or white noise	average ITI 180-s, RT30-s
Corbit & Janak					
exp1	0.1 ml 10% (v/v) ethanol	RR5 (1h)	16-P then 8-O	120-s Tone or clicker	average ITI 300-s, 6 CS+, 6 CS-, RT 30-s, US=0.2ml
exp2	0.1 ml 10% (v/v) ethanol	RR4 (1h)	10-P then 12-O	120-s white noise or clicker	average ITI 300 s, 6 ethanol, CS 6 sucrose CS, RT 30-s, US=0.2ml
Krank et al					
	0.1 ml 10% (v/v) ethanol	conc VI 20-s (0.5h)	O then 8-P	10-s cue light	average ITI 60-s, 20 CS presentations, US=0.2 ml
Milton et al					
	0.1 ml 10% (v/v) ethanol	VI 60-s (0.5h)	13-O then 11-P	120-s Tone or Clicker	average ITI 120-s, RT 30-s, 6 CS+ presentations with 2 CS- presentations on last training session
LeBlanc et al					
	0.2 mg Cocaine HCl	Heterogeneous chain RR4, RR4 (2 h)	4-P then 10-12-O	120-s Tone or clicker	average ITI 300-s, US=0.5 mg Cocaine at tone onset, 12 CS presentations; session before conditioning 12 CS- presentations

^AFR=Fixed Ratio, VI=Variable Interval, RR=Random Ratio, conc=concurrent

^BO=operant, P=Pavlovian, number = number of training sessions, when number is absent number training sessions was unclear

^CITI=Inter-Trial-Intervals between CS presentations, RT=Random Time schedule of US delivery, when US differed in magnitude from reinforcer used its size is provided