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# Habitual alcohol seeking: Neural bases and possible relations to alcohol use disorders

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## Abstract

Loss of flexible control over alcohol use may contribute to the development of Alcohol Use Disorders. An increased contribution of response habits to alcohol- related behaviors may help explain this loss of control. Focusing on data from outcome devaluation and Pavlovian-instrumental transfer procedures, we review evidence for loss of goal-directed control over alcohol seeking and consumption drawing from both preclinical findings and clinical data where they exist. Over the course of extended alcohol self-administration and exposure, the performance of alcohol-seeking responses becomes less sensitive to reductions in the value of alcohol and more vulnerable to the influences of alcohol-predictive stimuli. These behavioral changes are accompanied by a shift in the corticostriatal circuits that control responding from circuits centered on the dorsomedial to those centered on the dorsolateral striatum. These changes in behavioral and neural control could help explain failures to abstain from alcohol despite intention to do so. Understanding and ultimately ameliorating these changes will aid development of more effective treatment interventions.

### Keywords

outcome devaluation; Pavlovian-instrumental transfer; ethanol; dorsal striatum; stimuli; habit learning

## Introduction

While alcohol use for many is driven by the positively reinforcing effects of the drug, problem use and addiction can develop. This can largely be defined as a loss of flexible control over drug use. Indeed, the diagnostic criteria for Alcohol Use Disorder (AUD) include unsuccessful efforts to control alcohol use and persistent use despite a variety of

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negative outcomes related to ongoing alcohol use. Thus, it is not just alcohol use itself, but rather the struggle to control it that defines an AUD. For treatment interventions to succeed, it is of great importance to understand why control is so difficult.

One proposed explanation is that over the course of extended use, alcohol-related behaviors become more ingrained and automatic thus establishing a *drinking habit*. While this term is routinely used colloquially, in recent years there has been a concerted effort and a growing number of studies to formally examine the concept of a drug habit and the utility of this framework for understanding addiction. The purpose of this review is to summarize these findings, evaluate the evidence for habitual control over alcohol seeking as well as limitations of this model, and to highlight areas for future research.

## Defining goal-directed actions and response habits

In early use, or for casual users, alcohol is consumed for its positive reinforcing properties. However, over time and with repeated use, alcohol seeking and use become progressively independent of the drug's immediate rewarding properties. While negative reinforcement mechanisms may play an increasing role with excessive use and particularly in cases of alcohol dependence (this literature is reviewed extensively elsewhere; e.g., Koob, 2013) there is a distinct idea that behavior becomes dissociated from its direct consequences, either positive or negative. This idea that behavioral control becomes detached from the outcomes produced by performance of a particular response conceptually and operationally captures the definition of habits. Because most recreational drug and alcohol use starts as a flexible behavior, it is unclear at what point control shifts to a habit-based system and whether this is uniform across different individuals. Indeed, there is growing appreciation of the fact that diverse factors may lead to problem alcohol use for different individuals (Litten et al., 2015) and there may be individual differences in the role of habits in controlling behavior. Therefore, it is essential that we are able to identify whether alcohol-seeking responses are flexible actions or response habits. Behavioral procedures such as outcome devaluation have been developed and successfully implemented in both animal models and human subjects to assess whether behavior is goal-directed or not. These behavioral procedures allow habits to be operationalized and identified.

## Outcome devaluation reveals performance control

Flexible, goal-directed performance relies on an expectancy related to the outcome of a particular action and thus involves both knowledge of response-outcome contingencies and evaluation of the current value of the goal or outcome of responding. As such, goal-directed behavior tracks the current value of that outcome and is normally reduced when outcome value is decreased or if the relationship between responding and outcome delivery is broken. In contrast, habitual responding is not directly controlled by outcome expectancy, rather these behaviors rely on previous reinforcement history and are automatic or elicited by antecedent stimuli, that is, they occur in the presence of familiar stimuli or circumstances where the behavior has been performed and reinforced many times in the past. When responding is habitual, because we (or experimental animals) act without evaluation of the immediate consequences of our behavior, changes in the value of the rewarding outcome

have no immediate effect on performance of that response (Adams, 1982; Dickinson, 1985; Corbit, Nie & Janak, 2012). This idea can be captured experimentally; by specifically manipulating outcome value and observing consequent effects on performance, outcome devaluation tests provide a useful tool for identifying goal-directed versus habitual responses.

## Sensitivity to stimulus influences

While habits have been largely defined as instances where goal-directed control fails, habit learning is proposed to rely on an independent learning process: habits are triggered by environmental stimuli that have previously become associated with the response, that is, they are based on stimulus-response (S-R) learning. Thus, positive evidence for habitual control can be obtained by examining the influence of Pavlovian stimuli in promoting and directing responding. Indeed, there is a substantial literature indicating that environmental stimuli that act as reminders of previous alcohol use can trigger subjective craving, or activate neural systems that control alcohol-seeking outside conscious awareness, and thus may contribute importantly to relapse risk (Grusser et al., 2002; Le & Shaham, 2002; Loeber et al., 2006; Fox et al., 2007; Sinha et al. 2009). Of note, whether the responding driven by these stimuli is goal-directed or habitual has rarely been assessed. Furthermore, the evidence that cue-induced craving predicts alcohol use is at best mixed (Carter & Tiffany, 1999; Tiffany & Conklin, 2000).

Rather than assessing craving directly, other procedures that examine stimulus-driven behavior can be used; one example is known as Pavlovian-instrumental transfer (PIT). An advantage of this procedure is that it directly measures the influence of stimuli on responding without relying on intermediary processes such as craving. In addition, this procedure can be used in humans as well as experimental animals. This task typically involves three stages. In the first, Pavlovian conditioning is conducted pairing a stimulus or a number of stimuli with an outcome or outcomes (such as food, alcohol or monetary reward). In the second stage, instrumental conditioning is conducted in which one or more instrumental actions, such as a lever-press response, are trained, typically using the same outcomes presented in stage one but now in the absence of any Pavlovian stimuli. In the final test stage evidence of PIT is examined by making the instrumental actions available and, for the first time, periodically presenting the Pavlovian stimuli thus allowing their influence on instrumental action to be assessed. The influence or transfer of control by the Pavlovian stimuli onto instrumental performance constitutes the Pavlovian-instrumental transfer effect.

Depending on the details of the training conditions, a stimulus may produce an enhancement (or suppression) of responding as a result of the arousal that the stimulus elicits through its association with reinforcement generally (referred to as general transfer). Alternatively, a stimulus may have outcome-specific effects selectively increasing only responses associated with the same outcome as is predicted by the stimulus (referred to a specific transfer). As such, some theoretical accounts suggest that stimuli act to produce an expectancy regarding a particular outcome that, through a form of S-R process (S-O-R), could elevate the performance of an associated action (e.g., Trapold & Overmier, 1972; Corbit & Balleine, 2005). Importantly however, the ability of stimuli to trigger responding does not depend on

the predicted outcome being valuable at the time of testing. Specifically, the ability of a stimulus to augment the performance of an action predicting the same outcome as the stimulus is not altered by outcome devaluation (Rescorla, 1994; Watson et al., 2014), although baseline response rates may be reduced. Similarly, PIT effects also survive a number of manipulations that degrade the stimulus-outcome (S-O) contingency. For example, outcome-specific PIT is preserved following extinction of the S-O association, pairing of the stimulus with an alternate outcome, and a switch to either a random or explicitly unpaired S-O contingency following initial training (Delamater, 1996). These results are consistent with other recovery phenomena (spontaneous recovery, renewal and reinstatement) that demonstrate that S-O associations and their influence on behaviour are difficult to permanently undermine once established. These types of findings provide evidence of a dissociation between the ability of Pavlovian stimuli to invigorate responding and an evaluative process concerned with the consequences of that responding, consistent with our definition of habitual behavior. Furthermore, the ability of stimuli to drive behavior as measured by PIT increases under conditions that promote habitual control, defined using the devaluation task - for example, following extended training (Holland, 2004) or drug exposure (Sadoris et al., 2011; LeBlanc et al., 2013) -- supporting the idea that this is a valid measure of habitual responding.

## Experimental studies of alcohol and habit learning

### Studies of outcome devaluation

Using the outcome devaluation procedure, alcohol-seeking was shown to shift from goal-directed to habitual over the course of extended alcohol self-administration (Corbit, Nie & Janak, 2012). In this task (Figure 1), experimental subjects are first trained to perform a particular response, such as pressing a lever, which leads to the delivery of a specific outcome - in this case, alcohol. Once stable responding is established, the value of the outcome is manipulated either by pairing consumption with illness (conditioned taste aversion) or simply by allowing consumption of the outcome until satiety is achieved (outcome-specific satiety). So, for example, rats may be allowed to freely drink alcohol for one hour in the home cage, thus decreasing the immediate value of alcohol relative to a control condition where they are pre-fed a different outcome (e.g., sucrose). Performance of the response that previously earned alcohol is then tested in extinction to determine if the subject utilizes information about the modified value of the outcome. If responding changes in concordance with the modified value of the outcome, then performance is said to be goal-directed. If responding is insensitive to changes in outcome value and continues despite devaluation, this provides evidence for habitual performance.

We have shown that alcohol-seeking is flexible after limited instrumental self-administration training (2 weeks); that is, rats decrease responding following devaluation. In contrast, after extended training (8 weeks), responding for alcohol no longer shows sensitivity to changes in outcome value, the hallmark of automatic or habitual performance (Corbit, Nie & Janak, 2012; 2014). This effect appears to be due to the impact of chronic exposure to alcohol, because rats given equivalent extended alcohol exposure in the home cage but trained to respond to earn sucrose reward also failed to show sensitivity to devaluation, in contrast to

subjects responding for sucrose who did not receive pre-exposure to chronic alcohol (Corbit, Nie & Janak, 2012). Similarly, multiple cycles of chronic intermittent exposure (CIE) to alcohol using vapor chambers can decrease sensitivity devaluation produced by pairing alcohol with illness produced with lithium chloride (Lopez, Becker & Chandler, 2014).

Other animal studies have also found evidence for habitual responding for alcohol; these studies have generally used interval schedules of reinforcement to encourage habitual responding, based on early work demonstrating that limited training on interval schedules, but not ratio schedules, promotes habitual responding (Dickinson, Nicholas, and Adams, 1983). These studies have found that responding for alcohol on interval schedules is insensitive to devaluation produced by pairing alcohol with lithium chloride-induced illness (Barker et al., 2010; Dickinson, Wood and Smith, 2002; Mangieri et al., 2012). Of note, when satiety is used to devalue alcohol, animals are likely to be intoxicated at the time of testing; in contrast, conditioned taste aversion produced with lithium chloride is established over days, usually in a separate apparatus, and animals are alcohol-free for the critical test day. The consistent results using the two methods suggest that loss of sensitivity to devaluation is not readily explained by factors such as acute intoxication or tolerance.

The use of interval schedules allows the convenience of testing for habitual responding after a much shorter training period than with ratio schedules. One advantage of this approach is that experiments can be designed with two groups, one group trained on an interval schedule and the other on a ratio schedule, to allow direct comparison of experimental manipulations on habitual and goal-directed behavior, respectively. A second advantage in this approach is that training time and alcohol exposure history can be equated across both reinforcement training procedures. However, the use of interval schedules to promote habitual responding fails to capture the gradual progression from goal-directed to habitual behavior over time with repeated performance of the same behavior that results in increasing cumulative drug exposure – an essential feature of the notion of habitual drug and alcohol use in humans. Thus, comparisons of behavior early and late in training under ratio schedules of reinforcement maintain strong face validity with drinking behavior in humans. Nonetheless, while the rapid onset of schedule-induced habits may not capture all aspects of human drug use, the extant data suggest that the neural substrates mediating drug-promoted habits, those produced by overtraining or schedule promoted habits are largely overlapping. As such, schedule-induced habits may still be a valid model for investigation of neural substrates, although more research on this matter is needed.

The above studies provide evidence for habitual responding for alcohol, by definition specifically focused on alcohol-seeking actions, not consumption. Related studies found that the oral intake of alcohol itself can also become insensitive to devaluation. For example, both consumption and motivation to respond for alcohol are decreased by the addition of the bitter tastant quinine following limited alcohol exposure, but this sensitivity is reduced following extended alcohol exposure (e.g. Lesscher et al., 2010; Hopf et al., 2010). While it is not clear what behavioral mechanisms underlie these demonstrations of insensitivity of alcohol intake to quinine adulteration, it is possible that the sensory (taste) features of alcohol come to act as a stimulus promoting further alcohol seeking and drinking, through outcome-response associations (Balleine and O'Doherty, 2010).

Related tasks that are conceptually similar to devaluation studies, but that target the response-outcome association rather than outcome value have also shown that alcohol self-administration is more prone to habitual control relative to sucrose self-administration (Mangieri et al., 2014). For example, following initial training where a lever-press response delivers alcohol, if the contingent relationship is reversed such that a lever press delays otherwise freely delivered alcohol, animals trained to self-administer alcohol under interval schedules are less sensitive to this contingency degradation than animals trained under ratio schedules. Notably, sucrose-trained animals are able to adjust to the new contingency regardless of the schedule of reinforcement used in training (Mangieri et al., 2014).

Thus, taken together, there is compelling evidence that extended alcohol exposure produces behavior insensitive to changes in outcome value or probability. Importantly, not only do alcohol-seeking behaviors become habitual, but alcohol exposure can affect performance of responses reinforced with other rewards, e.g. sucrose in rodent studies or money in human studies (Corbit et al, 2012; Hogarth et al., 2012; Sjoerds et al., 2013; Garbusow et al., 2014). Such findings are important because they demonstrate that in addition to leading to habitual control over drug seeking, exposure to alcohol can have a broader effect on decision making and cognitive control likely due to adaptations in the neural circuits that underlie these forms of learning (see below).

## Studies of stimulus influences

The ability of alcohol-paired cues to invigorate and direct alcohol seeking can be measured using PIT, as mentioned above. In rats trained that a discrete auditory cue predicts alcohol delivery, presentation of that same auditory cue in the presence of a lever that previously earned alcohol increases responding (Corbit & Janak, 2007). This result is expected based on previous studies with non-drug reward. However, the alcohol-predictive cue surprisingly also increased responding on a second lever that previously earned sucrose. From this, it appears that alcohol cues invigorate reward seeking in a general way that does not take into account the specific outcome of responding, in line with outcome-independent habitual control of responding. This contrasts with the typical outcome-specific manner in which cues paired with non-drug reward increase reward seeking (Glasner et al., 2005; Corbit & Janak, 2007). It is perhaps not surprising that general rather than specific PIT effects are generated by an alcohol-predictive stimulus given that alcohol also promotes habitual responding, as this learning relies on reinforcement but not specific aspects of the outcome. Alternatively, if goal-directed control is compromised due to impaired inhibitory control following extended alcohol exposure, the general influence of an alcohol-predictive stimulus could be explained by failure to inhibit stimulus influences where inappropriate (i.e., when the available response earns sucrose, rather than alcohol).

A recent demonstration of the relationship between alcohol cues and habitual responding supports an effect on responding that is alcohol outcome independent; when subjects were tested in an alcohol-paired context, instrumental responding for food reward became habitual and insensitive to devaluation, whereas when the same subjects were tested in a neutral context, their behavior was goal-directed (Ostlund et al., 2010). This suggests that

simply being exposed to alcohol-paired stimuli and contexts promotes a shift from goal-directed to habitual behavior.

Evidence from non-drug rewards suggests that Pavlovian cues enhance habitual responding preferentially, or to a greater extent, as compared with goal-directed responding, indicating a progressive increase in the impact of cues over training (Holland, 2004). However, there is also evidence suggesting that greater responding to food-paired cues prior to alcohol training is related to faster development of habitual responding for alcohol (Barker et al., 2014). On the other hand, the relative effectiveness of PIT with food reinforcement tested prior to instrumental training for alcohol was not predictive of development of habitual responding for alcohol (Barker et al., 2014). As well, after sixteen days of intermittent alcohol exposure in a vapor chamber, no evidence of PIT in mice trained with food reinforcement was observed (DePoy et al., 2015). In both of these cases, the Pavlovian cues were not alcohol paired, which may explain the findings.

Of note, rats trained within a Pavlovian alcohol conditioning procedure that allows for separate measure of cue-directed (sign-tracking) and alcohol-directed (goal-tracking) conditioned responses found that rats come to exhibit greater sign-tracking than goal-tracking (Srey et al., 2015), and sign-tracking is a stimulus-directed behavior response that is insensitive to outcome devaluation (Morrison et al., 2015).

## Translation of the model

While the behavioral paradigms discussed above were developed within animal models, they have been effectively used in human subjects including clinical populations (see Balleine & O'Doherty, 2010; Griffiths et al., 2014; Sjoerds et al., 2013; Garbusow et al., 2014; 2015). Further, consistent with the framework presented above, it has been suggested that human drug and alcohol use is likewise controlled by both cognitive and non-cognitive (automatic) processes (Tiffany, 1990; Tiffany & Conklin. 2000). Although individuals with AUDs might experience intense desire for alcohol, which could be considered exaggerated valuation, routine aspects of obtaining and using alcohol might become automatic or habitual with repeated practice, suggesting that multiple cognitive processes contribute to drug-seeking behaviors. Thus, the development of automaticity of alcohol seeking seen in the current model and the apparent separation of performance from evaluation might capture some aspects of the addictive process.

The cognitive processing model proposes that drug use in addiction is driven largely by automatic processes (Tiffany & Conklin, 2000), consistent with our view of habits. Recently there has been progress in experimentally evaluating whether human behavior is automatic or not. For example, a recent study using the devaluation task found that the reliance on a S-R habit strategy is increased in alcohol dependent patients compared to healthy controls and that these patients are less sensitive to devaluation (Sjoerds et al., 2013). Of note, in that study the tendency to rely on a habitual strategy when acquiring a new behavioral response was assessed using monetary reward and therefore is not specifically related to alcohol use but instead implicates an overall shift in behavioral control. Further, there is evidence of decreased activation of brain areas shown previously to be involved in goal-directed control

such as the ventromedial prefrontal cortex and anterior putamen (Valentin et al., 2007; Tricomi et al., 2009; deWit et al., 2012). Whether these decreases are the result of prolonged alcohol use or reflect predisposing traits that promote the development of alcohol use disorders is unknown and is an important question for future prospective or longitudinal studies.

Other studies using PIT provide evidence of enhanced stimulus control of behavior in alcohol users. For example, PIT effects are observed in both social drinkers (Martinovic et al., 2014) and detoxified alcoholics (Garbusow et al., 2014). In social drinkers, beer cues biased responding toward a response that earned beer thus providing some evidence of a selective PIT effect that promotes drinking behavior (Martinovic et al., 2014). Garbusow and colleagues (2014) examined PIT in recently detoxified alcoholics and found that the patient population was more likely to show a PIT effect and that when observed, the effect was stronger than in healthy controls. Interestingly, in that study, subjects were trained to respond for monetary reward and so the observed results, as described for devaluation above, suggest that alcoholics are more susceptible to the influence of Pavlovian stimuli, demonstrating altered decision-making processes that are not limited to behaviors directed towards alcohol. Intriguingly, evidence that PIT relates to addiction comes from the recent report that the strength of PIT effects is an indicator of relapse risk (Garbusow et al., 2015). In this study, fMRI analyses were conducted during PIT and patients were followed up for three months after testing. Recently detoxified alcoholics showed a stronger behavioral PIT effect than healthy controls as shown previously. Of interest, the activation of the NAc during PIT was greater in patients that went on to relapse, than in those that successfully abstained or in healthy controls. While the PIT design in this experiment also used monetary rather than alcohol, other work has implicated NAc activation in humans in cue reactivity and relapse (Heinz et al., 2004; Beck et al., 2012) and approach to alcohol cues (Wiers et al., 2014). Thus, these results suggest that PIT, as an index of susceptibility to Pavlovian influences, may prospectively help identify patients at greater risk for relapse. Direct effects of stimuli on an alcohol-seeking response would be of significant interest for future study. Further, where possible within the limits of fMRI resolution, additional information about subregions of the NAc as well as the role of other neural structures would also be of interest and may help identify the type of PIT that is generated (Corbit & Balleine, 2005; 2011).

It is interesting to consider the relationship between habitual and compulsive conceptualizations of alcohol seeking. Indeed, drinking may be viewed as compulsive, that is, driven by intense urges to seek and/or consume alcohol rather than being habitual and divorced from outcome value. It has recently been suggested that compulsive behavior is not necessarily driven by heightened value, but that dysregulation of control and failure to inhibit inappropriate responses rather than exaggerated assignment of value drive compulsive responses (Gillan et al., 2015). This could account for self-reported awareness of the value or cost of behaviours and/or the outcomes produced alongside failure to appropriately regulate these very behaviors. Both habitual and compulsive behaviours are insensitive to feedback from consequences and can continue despite self-reported awareness of the low value of the outcome produced and may not be incompatible descriptions of excessive alcohol use.

## Mechanisms

### Insight from neuroantatomical control of actions and habits

While behavioral data suggest increasing dominance of habitual responding following prolonged alcohol exposure, insight into how alcohol promotes this shift comes from an understanding of the neuroanatomical control of actions and habits, and the effects of alcohol on these circuits. Details of the anatomical control of actions and habits, including alcohol habits have been the focus of several recent reviews (Balleine & O'Doherty, 2010; Barker & Taylor, 2014; Barker, et al., 2015; Everitt and Robbins, 2016) and growing consensus points to the dorsomedial striatum (DMS; or head of the caudate in humans) and associated circuitry as being essential for goal-directed action whereas parallel corticostriatal circuitry centered on the dorsolateral striatum (DLS; or putamen in humans) is essential for habitual responding. A shift in control from DMS to DLS accompanies the transition to habitual control of alcohol seeking (Corbit et al., 2012). This can be seen by manipulating the function of each region early versus late in training. Temporary pharmacological inactivation of the DMS impairs responding after 2 weeks of alcohol self-administration but is without effect after 8 weeks of training. In contrast, pharmacological inactivation of the DLS is without effect following two weeks of training but, following 8 weeks of training when behavior is habitual (i.e. insensitive to devaluation), inactivating the DLS restores sensitivity to devaluation demonstrating that this region is required for the expression of response habits.

What remains less understood is how alcohol intake impacts this transition in control from the DMS to the DLS. The development of goal-directed and then habitual responding for natural rewards, as well as for skill learning in general, may be related to long-term dopamine-dependent changes in efficacy of excitatory inputs onto medium spiny neurons (MSNs) of the DMS and DLS (see Jin and Costa, 2015, and Lovinger et al., 2010, for review). Accumulating evidence suggests that chronic alcohol alters excitatory synaptic plasticity onto MSNs in both the DMS (Wang et al. 2007; 2015) and the DLS (DePoy et al., 2013, 2014); chronic alcohol-induced changes in GABAergic input to MSNs has also been reported (Wilcox et al., 2014). These synaptic plasticity changes may be related to alcohol-induced alterations in important components of intracellular signaling pathways that are distinct for the DMS and the DLS (for review see Ron and Messing, 2013). For example, there is an increase in STEP phosphorylation, an effect that decreases its activity, in mouse DMS after chronic alcohol consumption, that is not observed in other striatal regions, the DLS or the NAc (Darcq et al., 2014). Likewise, changes in expression of the neurotrophic factor, BDNF, occur in the DLS, but not DMS (Jeanblanc et al., 2009, 2013). Thus, there is physiological and molecular evidence that chronic alcohol functionally alters DMS and DLS circuitry. Collectively, the findings show distinct patterns of neuroadaptations to alcohol across striatal regions. In addition, alcohol-induced alteration of dopaminergic input to the dorsal striatum (c.f., Vena and Gonzales, 2015) may also interact with the above changes to impact learning-related plasticity.

Of note, inactivation of the DLS also impairs PIT for natural reward (Corbit and Janak, 2009), but alcohol PIT dependence upon DLS remains to be demonstrated. However, the

ventral striatal region, the NAc, is required for PIT for alcohol cues (Corbit et al., 2016), and this region is also implicated in the direct reinforcing effects of alcohol (Englemann et al 2009; Rewal et al., 2012); it is not clear whether or how dependence upon the NAc for PIT or alcohol reinforcement in may change over time.

The shift from DMS to DLS for control of alcohol seeking fits within a larger framework proposed to underlie changes in drug seeking behavior in addiction more broadly, in which a ventral-to-dorsal striatal shift is the basis for the development of addiction-like behavior, based on studies primarily with cocaine (Everitt and Robbins, 2005; Belin & Everitt, 2008). This and related conceptions posit that the development of habitual responding may be a necessary precursor to compulsive responding, often operationally-defined for laboratory experiments as responding that continues in spite of negative consequences. This is in accord with the tendency in AUD and other substance use disorders for behaviors to persist despite negative consequences and the substantial overlap between the neural substrates of goal-directed and habit learning and those that underlie compulsive disorders (Voon et al., 2015). Animal models of compulsive alcohol and drug seeking have in some cases been shown to involve the DLS (Jonkman et al., 2012), in agreement with this idea. However, excessive expression of habits could result from either direct strengthening of S-R associations and plasticity in underlying circuits or by diminished capacity to control the expression of habits, perhaps due to dysregulation of neural substrates involved in goal-directed learning and executive control (Gillan et al., 2015). The literature on the neural control of obsessive compulsive disorder links overreliance on habits with hyperactivity in the caudate and PFC rather than altered function of the putamen as neural correlates of the disorder. This is consistent with habits formed after drug-exposure; while intact DLS is necessary for expression of habit-based responding there is some evidence that drug-induced habits may result from altered function in the goal-directed system that alters subsequent learning and that DLS control is compensatory (Corbit et al., 2014).

The effects of alcohol on neural systems are, of course, not limited to striatal regions. The medial prefrontal cortex is involved in the acquisition of goal-directed behaviours in both rats (Balleine & Dickinson, 1998; Corbit & Balleine, 2003) and humans (Tanaka et al., 2008; Valentin et al., 2007). Drug- and alcohol-induced neuroadaptations in cortical regions, such as the medial prefrontal and orbitofrontal cortices, that project to striatal regions may also underlie the emergence of compulsive behavior (Jenstch and Taylor, 1999; Lucantonio et al., 2014). Indeed, it may be that the disruption of prefrontal cortical function impairs goal-directed behavior and the ability to flexibly switch from habitual to goal-directed responding as appropriate, thereby rendering drug seeking compulsive (Everitt and Robbins, 2015; Lucantonio et al., 2014). Further, the reduction of associated executive functions, particularly inhibitory control, may result in unwanted habitual behaviours being more difficult to suppress thus further diminishing flexible behavioral control. Amygdala regions may also critically contribute to the expression of goal-directed and habitual behavior, and perhaps the transition from one to the other as shown recently for cocaine (Murray et al., 2015). The basolateral amygdala is important for assigning motivational significance to stimuli based on sensory-specific properties, and damage to this structure impairs sensitivity to outcome devaluation and outcome-specific PIT (Corbit & Balleine, 2005). The central amygdala is involved in general PIT (Corbit & Balleine, 2005) as well as habit learning via

indirect connections (likely via the substania nigra) with the DLS (El-Amamy & Holland, 2007; Lingawi & Balleine, 2012). Amygdala abnormalities, including altered structure and function, are associated with alcohol dependence and may result in disinhibition of central amygdala targets and behavioural output (Gilpin et al.,2015). Altered central amygdala function following chronic alcohol use could promote the accelerated formation of response habits and general PIT, despite specific training, observed in alcohol self-administration models (Corbit & Janak, 2007) although the precise mechanism of any such effects is currently unknown. A further contributor could be alterations in dopaminergic learning signals (reward prediction error), that may hasten the shift from DMS to DLS (Keiflin and Janak, 2015). The circuit mechanisms underlying these shifts for cocaine, alcohol and other drugs is a major focus of current work (for review, Creed and Luscher, 2013; Everitt and Robbins, 2016; Keiflin and Janak, 2015). The hope is that the detailed understanding of the neurobiological substrates of actions and habits may aid the development of pharmacological interventions that reduce habits to promote flexible control.

## Implications for treatment

It is becoming increasingly recognised that AUD is heterogeneous; multiple neurobiological and/or environmental factors may contribute to development of problem drinking and it is unlikely that a single treatment will be optimally effective for all individuals (Litten et al., 2015). The role of habits is an important domain to consider within this context. We do not assume that habitual processes will explain all problem alcohol use; however, understanding the behavioral, neural and pharmacological control of habits could improve treatment outcomes, at least in those individuals showing evidence of habitual control of alcohol-related behaviors.

The disconnection of behavioral control from the value of alcohol captured in both outcome devaluation and PIT paradigms demonstrates that behavior can be driven by processes that rely on learning but are independent of desire which has implications for treatment approaches. For example, two of the current FDA approved pharmacological treatments for AUD aim to reduce the rewarding properties of alcohol (e.g. naltrexone or disulfram). As such, these are essentially outcome devaluation techniques and as reviewed above, mounting evidence suggests that alcohol exposure reduces sensitivity to such manipulations. Thus the therapeutic utility of this treatment strategy may be reduced, at least for those demonstrating heightened habitual control where outcome value is not the primary determinant of behavior. In contrast, acamprosate, another approved pharmacotherapy, targets craving. When someone is experiencing craving, alcohol should be highly valued; the dissociation of habitual behavior from value suggests is unlikely that habitual behaviors are associated with craving, and acamprosate may not be effective for altering habits, which could relate to its modest efficacy (Carter & Tiffany, 1999). Instead, drugs that improve cognitive performance may help reinstate goal-directed control. Further, behavioral therapies that diminish the effects of stimuli (e.g., extinction-based treatments) and promote evaluative process (e.g., awareness training) may be effective. Finally, deeper understanding of the neurobiological control of habits and failure of goal-directed control may yield novel pharmacological approaches to treatment.

## Limitations and Future Directions

Outcome devaluation and PIT tasks can reveal when behavior is under habitual control, which may aid understanding of decision-making deficits in alcohol use disorders. However, more research on this topic is needed to address the following issues.

Continued preclinical work strengthening the connection between the demonstrated neuroadaptations in striatal circuits following chronic alcohol and the development of habitual behavior is essential. Many of these changes have been shown to impact alcohol self-administration in rodent models. Thus, we know that alcohol alters striatal circuits in multiple specific ways, and that these alterations impact alcohol intake, but the specific behavioral mechanisms (i.e., goal-directed or habitual/compulsive responding) remain to be elucidated. Furthermore, although we have focused on data demonstrating a shift from goal-directed to habitual control of alcohol behaviors, whether this shift is the result of direct strengthening of habit learning and underlying circuits or impairment in goal-directed control has not been exhaustively investigated.

Regarding clinical application, the primary issue is whether habitual behavior related to alcohol use occurs in humans with AUDs. Thus, while the use of the procedures described herein in animal models and healthy human subjects is well established, more research in clinical samples, and particularly in treatment-seeking individuals, will be important. Intriguingly, initial studies in alcoholics support the view that habitual control may be an obstacle to recovery but this clearly needs to be further substantiated.

In a related point, while identifying when behavioral control is habitual is an important step, it remains to be established whether treatments that target these cognitive processes will be effective. This is an important area for future research.

Of course, multiple psychological and neural processes underlie AUDs. Increased habitual control may explain problem drinking and relapse despite desire to abstain from alcohol in only a subset of patients. Nonetheless, relatively simple behavioral tasks such as devaluation and PIT may help identify at risk populations, and help inform what type of treatment might be most effective. A further important direction is to determine whether a predisposition to rely on habit-based strategy confers greater risk for escalation of alcohol use and development of an AUD or whether the long-term effects of alcohol produce this effect. While preclinical data suggest that alcohol exposure alone can promote reliance on habits, clinical studies to address this question will be important and could inform preventative vs. corrective approaches to treatment.

## Summary and Conclusions

It has been suggested that over the course of extended use, drug-associated behaviors become habitual (Everitt and Robbins, 2005; 2016), mediated by automatic action schemas triggered by cues associated with previous drug use (Tiffany, 1990). Indeed, pre-clinical data has demonstrated that rats given extended alcohol self-administration or consumption in the home cage more readily form habits defined as a lack of sensitivity to outcome devaluation (Corbit et al., 2012; 2014, Barker et al., 2015). From this point of view, while alcohol is

initially sought for its rewarding properties, following extended use, alcohol seeking transitions to habitual control that is independent of the immediate value of the drug. Stimuli play a particularly important role in habitual behaviors since, as demonstrated by outcome devaluation procedures, the expression of habits does not rely on an expectation of the outcome a particular response produces but rather is triggered by environmental stimuli that over time have come to predict that responding will be reinforced under those environmental conditions. Indeed, the influence of stimuli has been shown to grow in parallel with the development of habitual control (Holland, 2004).

The evidence reviewed suggests that the role of habits is increased following extended alcohol use. The dissociation of alcohol seeking behaviors from evaluative processes may help explain why control of alcohol use becomes difficult even when an individual wants to change their behavior, and why relapse rates for alcohol use disorders are high. This is not to say that an alcoholic is not aware that they are drinking when they relapse. However, through the activation of a series of highly automatized or habitual behaviors, initially provoked by stimuli rather than conscious evaluation of or desire for the outcome those behaviors would ultimately produce, the expression of habits may place alcoholics in vulnerable situations, difficult to control, and highly likely to result in alcohol consumption. Thus, while habit learning may only explain some aspects of addictive behavior, or relate to a subset of the population with AUDs, understanding diminished deliberate control over use as well as an exaggerated influence of stimuli, could provide considerable insight into relapse, and identify cases where behavior change, namely alcohol abstinence, may be difficult. In addition, identifying if behavior is habitual might aid the development of more effective treatments and help inform which type of treatment is most likely to be effective.

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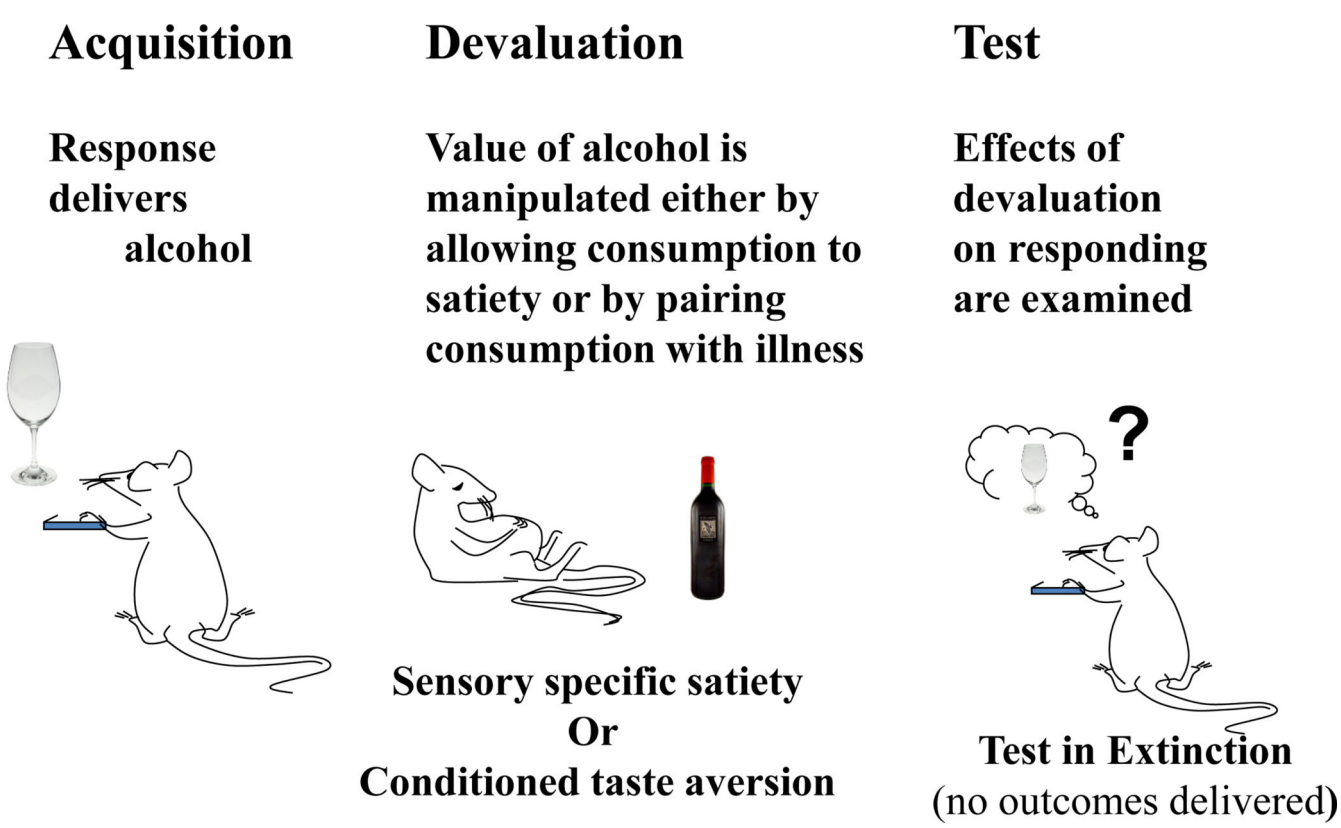


**Figure 1.**
Illustration of outcome devaluation procedure, used to determine whether responding is goal-directed or habitual