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Corticostriatal circuitry and habitual ethanol seeking

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Abstract

The development of alcohol-use disorders is thought to involve a transition from casual alcohol use to uncontrolled alcohol-seeking behavior. This review will highlight evidence suggesting that the shift toward inflexible alcohol seeking that occurs across the development of addiction consists, in part, of a progression from goal-directed to habitual behaviors. This shift in "response strategy" is thought to be largely regulated by corticostriatal network activity. Indeed, specific neuroanatomical substrates within the prefrontal cortex and the striatum have been identified as playing opposing roles in the expression of actions and habits. A majority of the research on the neurobiology of habitual behavior has focused on non-drug reward seeking. Here, we will highlight recent research identifying corticostriatal structures that regulate the expression of habitual alcohol seeking and a comparison will be made when possible to findings for non-drug rewards.

Keywords

Habit; goal-directed behavior; alcohol; prefrontal cortex; dorsal striatum; nucleus accumbens; orbitofrontal cortex

Introduction

Identification of the neurobiological substrates of habitual ethanol seeking may help to guide the development of novel therapeutic strategies that can enable restoration of behavioral control. While reducing ethanol-seeking habits is not expected to be a stand-alone cure for addiction, or a solution for all individuals with alcohol-use disorders, the ability to restore cognitive control over ethanol-seeking behaviors may enable traditional therapeutic

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strategies. Despite the applicability of this model to addictive behavior (Everitt, 2014; Kalivas, 2008), a preponderance of the research into the neuroscience of habitual behavior has been performed with models of non-drug reward seeking (e.g., Yin & Knowlton, 2006), rather than ethanol. While it can be argued that the structures mediating non-drug habits regulate the development of habitual behavior in general, recent work suggests that alcohol reinforcers may differentially engage the neurocircuits that control behavioral flexibility (Barker, Taylor, De Vries, & Peters, 2014; Corbit, Nie, & Janak, 2012; Mangieri, Cofresí, & Gonzales, 2012; Shillinglaw, Everitt, & Robinson, 2014). In this review, we will focus on the novel application and extension of these findings to the development of habitual ethanol-seeking behavior that, in part, characterizes alcohol-use disorders. We will provide a framework for the role of habitual processes in ethanol-seeking behavior and summarize findings presented at the 2014 Alcoholism and Stress Meeting in Volterra, Italy with the intention to highlight novel observations on the role for corticostriatal circuits in the regulation of ethanol-seeking behavior. (For a more in-depth review of the neuroanatomy of habitual processes in ethanol seeking, see Barker & Taylor, 2014, and O'Tousa & Grahame, 2014).

Modeling conditioned behavior in alcohol-use disorders

In recent years, there has been a burgeoning interest in understanding drug seeking that is not mediated by the immediate rewarding properties of drugs of abuse. Work in both animals and humans has suggested drugs of abuse, including alcohol, are sought not only for their positive rewarding properties, but also out of habit (Adams, 1982; Dickinson, Wood, & Smith, 2002; Robbins & Everitt, 1999). In other words, while drugs of abuse are initially sought for their rewarding properties, over time and with repeated performance, drug seeking transitions to habitual reward-seeking behaviors that are more independent of the drug's immediate rewarding properties. These habitual behaviors can be either self-initiated or elicited by environmental or interoceptive stimuli. This may contribute to compulsive drug seeking which occurs despite negative consequences of drug taking. This suggests that early drug-seeking behavior may be more goal directed and performed in relation to the expected rewarding effects via an expected action-outcome relationship. In contrast, habitual behavior is thought to be less sensitive to changes in outcome value or action-outcome contingency (Adams, 1982; Adams & Dickinson, 1981; Colwill & Rescorla, 1985; Dickinson, 1985). These working definitions led to objective methods for assessing instrumental response strategy. By manipulating either the action-outcome contingency (a method called contingency degradation) or outcome value (often through outcome devaluation methods), it can be determined whether an action is being performed in a goal-directed or habitual manner.

A significant literature implicates aberrant cue sensitivity and habit learning in addiction. In human addicts, drug-paired cues have been shown to elicit drug craving and motivate drug-taking and approach behaviors (Koob & Volkow, 2010; Pickens et al., 2011; Sinha & Li, 2007; Yoder et al., 2009). In rodent models, the ability of drug-paired cues to promote drug-seeking and relapse-like behaviors has been well established using conditioned place preference (for review see Tzschentke, 1998) and cue-induced reinstatement paradigms (McFarland & Kalivas, 2001). In addition, reward-paired cues have been shown to

invigorate instrumental reward seeking through the use of Pavlovian-to-instrumental transfer (PIT) paradigms.

While a majority of what is known about cue-mediated reward seeking has focused on non-drug rewards (e.g., sucrose) or psychostimulants, there is growing evidence that ethanol-paired cues may impact reward-seeking behavior in ways that differ from these reinforcers. For example, in a study of PIT (conducted under extinction conditions), when rats were trained that a discrete cue predicted ethanol delivery, presentation of that same cue in the presence of a lever that previously earned ethanol resulted in enhanced responding (Corbit & Janak, 2007). These observations suggest that the motivational properties of the alcohol-paired stimulus invigorated responding. This result is expected based on previous studies with non-drug reward. What was unique, however, about the alcohol-predictive cue was that when it was presented while animals had access to a lever that previously earned sucrose, sucrose-seeking behavior was also increased by the alcohol-predictive stimulus. Under particular training conditions, stimuli that predict a reward other than that earned by an instrumental response can also enhance instrumental responding – an effect known as general PIT. However, typically a stimulus that predicts a reward earned by another trained, but currently unavailable response does not increase and may even reduce responding (Corbit & Balleine, 2005; Nadler, Delgado, & Delamater, 2011). Thus, the finding that ethanol cues invigorate reward seeking in a general – potentially habitual – way, rather than in an outcome-specific manner, as is typical for cues paired with non-drug reward, is an important distinction between the effects of stimuli paired with alcohol compared to other rewards (Corbit & Janak, 2007; Glasner, Overmier, & Balleine, 2005). Furthermore, as general and specific PIT effects rely on independent neural circuits (Corbit & Balleine, 2005, 2011; Corbit, Janak & Balleine, 2007), the observed general effect of alcohol-predictive stimuli may indicate that alcohol-predictive stimuli recruit different neural substrates than stimuli paired with natural rewards. In addition, ethanol-paired contexts have been shown to render non-drug reward seeking insensitive to changes in outcome value (Ostlund, Maidment, & Balleine, 2010). This suggests that simply being exposed to ethanol-paired contexts promotes a shift from goal-directed to habitual behavior. While it is unclear how exposure to these cues and contexts drives the expression of habitual behavior, one attractive idea is that drug-paired cues impinge upon cognitive resources that may be necessary for the expression of goal-directed actions (e.g., Jentsch & Taylor, 1999; Tiffany, 1990).

Habitual behaviors are of particular interest in understanding persistent alcohol seeking that contributes to alcohol-use disorders. Indeed, alcoholics have been shown to have increased reliance on habit-like response strategies as well as activation of the neurocircuitry supporting habitual behavior, as compared to control subjects (Sjoerds et al., 2013). However, it is unclear whether these differences predate drug exposure and potentially represent increased risk for the development of alcohol-use disorders, or whether differences in response strategy selection in alcoholics result from chronic ethanol exposure itself. Importantly, work in animal models has demonstrated that there are both individual differences in risk for the formation of ethanol-seeking habits (Barker, Zhang, et al., 2014) as well as ethanol-induced changes in the development of habitual behaviors (Corbit et al., 2012). In particular, prior to any ethanol exposure, it has been shown that individuals with

high Pavlovian approach toward a food reinforcer also show rapid development of ethanol-seeking habits. This suggests that pre-existing differences in cue reactivity may predispose certain individuals toward loss of flexible ethanol seeking. Considerable evidence also indicates that ethanol itself may drive the development of habitual behaviors. Indeed, habitual control over ethanol self-administration has been shown to develop more rapidly than for non-drug reinforcers (Corbit et al., 2012; Dickinson et al., 2002). Recent work has also revealed that this is not due to the use of an ethanol reinforcer *per se*; indeed, self-administered alcohol is not always sufficient to promote habit formation (Hay, Jennings, Zitzman, Hodge, & Robinson, 2013; Samson et al., 2004; Shillinglaw et al., 2014). Instead, ethanol exposure can produce changes in the neural circuits encoding goal-directed and habitual behaviors that ultimately facilitate the transition away from goal-directed actions to habitual behavior (Corbit et al., 2012).

Regulation of reward seeking within the striatum

A significant literature has identified striatal subregions as critical regulators of reward-seeking behavior. While the ventral striatum is thought to be largely involved with cued outcome-mediated behaviors, the more dorsal aspects of the striatum appear to have distinct contributions to goal-directed and habitual reward-seeking behavior. The nucleus accumbens (NAc) can be subdivided into two primary subregions – the NAc shell and the core – with distinct network connectivity with the prefrontal cortex (PFC). The NAc shell receives extensive input from the more ventral infralimbic PFC, a structure known to be required for the expression of habitual behavior (Barker, Taylor, & Chandler, 2014; Coutureau & Killcross, 2003). The more dorsal prelimbic PFC, which plays a role in the acquisition of goal-directed actions (Killcross & Coutureau, 2003; Tran-Tu-Yen, Marchand, Pape, Di Scala, & Coutureau, 2009), more extensively innervates the NAc core. Though their precise roles differ, both the NAc core and NAc shell have been implicated repeatedly in the integration of reward information that is critical for the performance of Pavlovian and instrumental behaviors (Hart, Leung, & Balleine, 2014; O'Doherty et al., 2004). In particular, as with other reinforcers, NAc core and NAc shell inactivation differentially impact the effect of ethanol cues on behavior. For example, inactivation of NAc core, but not NAc shell, reduces conditioned responding for ethanol cues (Gremel & Cunningham, 2008), as well as renewal of responding in non-ethanol paired contexts (e.g., LaLumiere & Kalivas, 2008; Peters, Kalivas, & Quirk, 2009). Further distinction between subregions of the NAc was observed with presentation of contextual and discrete ethanol cues which produced a dopamine response in the border between core and shell, but not in either region by itself (Howard, Schier, Wetzel, & Gonzales, 2009). However, inactivation of either structure reduced cued lever-responding in an ethanol-paired context, suggesting that the NAc shell may play a larger role in context-mediated ethanol-seeking behavior (Chaudhri, Sahuque, Schairer, & Janak, 2010). Importantly, lesions of the NAc shell do not prevent the expression of goal-directed actions for natural rewards, as measured by either contingency degradation or outcome devaluation measures (Corbit, Muir, & Balleine, 2001). However, to our knowledge, it has not yet been determined how loss of the NAc impacts response strategy in animals that are performing habitual reward seeking for either non-drug or ethanol reinforcers.

The dorsomedial (DMS) and dorsolateral striatum (DLS) receive divergent, but overlapping, inputs from cortical and subcortical structures. The associative DMS receives extensive glutamatergic innervation from associative cortices (McGeorge & Faull, 1989; Pan, Mao, & Dudman, 2010; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004), while DLS is highly innervated by sensory motor cortices (McGeorge & Faull, 1989; Pan et al., 2010; Voorn et al., 2004). This dissociation in cortical inputs is mirrored in their apparent roles in goal-directed and habitual non-drug reward seeking – DMS is critical for the expression of goal-directed sucrose seeking (Yin, Knowlton, & Balleine, 2005; Yin, Ostlund, Knowlton, & Balleine, 2005), while DLS appears to be critical for the development and expression of habitual sucrose seeking (Yin, Knowlton, & Balleine, 2004, 2006). The majority of this research has investigated the contribution of these structures to the development of non-drug reward-seeking habits. However, exciting new work has highlighted the roles of these structures and circuits in the development of habitual ethanol seeking. Indeed, recent data indicate that treatments that decrease DLS function and/or output can restore goal-directed ethanol-seeking behavior (Corbit et al., 2012; Corbit, Nie, & Janak, 2014), suggesting an overlapping role for this structure for both non-drug and ethanol reinforcers.

To gain a greater understanding of the role of the DMS and DLS in both goal-directed and habitual ethanol-seeking behaviors, Fanelli and colleagues performed electrophysiological recordings from these structures in rats that had been trained to respond on one of two different reinforcement schedules – variable-interval or fixed-ratio – that engender habitual or goal-directed behavior, respectively (Fanelli, Klein, Reese, & Robinson, 2013). Under the fixed-ratio schedule, where animals are expected to seek the alcohol reward in a goal-directed manner, DMS neuronal activity increased after the operant response and during the presentation of alcohol-paired cues and alcohol delivery. In contrast, DLS neuronal activity increased prior to as well as during the operant response, and thus was associated with instrumental performance. Interestingly, in animals self-administering ethanol under a variable-interval schedule, the general patterns of activity in the DMS and DLS were less distinct: more DLS neurons exhibited excitations to alcohol reinforcement (cues and reward delivery) while more DMS neurons showed excitation to the motor response than were observed under the fixed-ratio schedule. Of interest, Fanelli et al. (2013) reported that more anterior DMS neurons exhibited excitation upon reinforcement under fixed-ratio (‘goal-directed’) conditions, while neurons that showed increased activity were more posterior in rats that had been trained on a habit-promoting schedule. Inactivation studies have shown that inhibition of either the anterior or posterior region of the DMS during training, but not during testing, impairs the acquisition of action-outcome associations required for goal-directed behavior toward non-drug rewards (Corbit & Janak, 2010). In contrast, excitotoxic lesions of anterior DMS made before instrumental training do not disrupt goal-directed behavior in animals trained to make an instrumental response, while lesions of posterior DMS do disrupt this behavior (Yin, Ostlund, et al., 2005). Notably, inactivation of posterior DMS at the time of testing similarly impaired the expression of goal-directed behavior. One interpretation of these results is that while both the anterior and posterior DMS contribute to goal-directed behavior, the anterior DMS is required during the acquisition of this response strategy. Additionally, when examined in the same mouse in a task shifting between goal-

directed and habitual actions, the same posterior DMS neuron would modulate activity more strongly during goal-directed than habitual actions, suggestive of an increased recruitment of DMS during goal-directed behaviors (Gremel & Costa, 2013). Supporting this hypothesis, many anterior DMS neurons were found to be phasically activated during alcohol-predictive cues, especially in rats employing a goal-directed behavioral strategy (Fanelli et al., 2013).

Striatal excitation to instrumental responses has also been reported for non-drug rewards and may be enhanced in response sequences (e.g., multiple lever presses) as opposed to single responses (Jin & Costa, 2010). While some studies have observed recruitment of DLS neuronal activation during habit formation (Kimchi, Torregrossa, Taylor, & Laubach, 2009), others have reported diminished activation as a motor task becomes well-learned (e.g., Tang et al., 2009). Notably, when the amount of training was equivalent and extensive (>6 weeks of training), rats performing under variable-interval or fixed-ratio schedules exhibited similar proportions of phasic firing of DLS and DMS neurons during ethanol reinforcement (Fanelli et al. 2013). This confirms that, similar to findings with non-drug reinforcers (Gremel & Costa, 2013), behavioral strategies do not arise from an “either-or” shift of neuronal processing between associative DMS and sensorimotor DLS circuits, but rather that they are both engaged during action selection, albeit with differential prominence to direct behavioral strategy.

In addition to extensive cortical innervation, both the DLS and DMS receive inputs from midbrain dopamine structures, and dopaminergic innervation of these striatal regions appears to be critical for the development of habitual behavior. Loss of dopaminergic innervation of the DLS has been shown to prevent the development of non-drug reward-seeking habits (Faure, Haberland, Condé, & El Massioui, 2005). In contrast, psychostimulant exposure appears to facilitate habit formation for non-drug rewards (Nelson & Killcross, 2006, 2013; Schmitzer-Torbert et al., 2015), as appears to be the case for ethanol exposure (Corbit et al., 2012). Furthermore, as is the case with ethanol, psychostimulant-facilitated habits appear to be dependent on the same neuroanatomical substrates as normal habit learning (Schmitzer-Torbert et al., 2015). This suggests that alterations in dopamine signaling in these targets may drive the development of habitual reward seeking. Investigation of the effects of psychostimulant exposure on habit formation has implicated dopamine signaling and has revealed that amphetamine facilitation of habitual behavior can be reversed through nonspecific or D1 dopamine receptor antagonism (Nelson & Killcross, 2013). Interestingly, the effect of amphetamine exposure appears to be exacerbated by DA D2 antagonism. This is consistent with reports demonstrating that D2 receptor function is reduced following chronic exposure to drugs such as cocaine (Volkow et al., 1993) and that resilience to cocaine use is accompanied by potentiation of glutamatergic inputs to D2 neurons (Bock et al., 2013). Related findings show that following chronic cocaine exposure, cocaine challenge produces a larger and more sustained calcium response in D1 than in D2 neurons in the dorsal striatum, suggesting that disrupted balance between direct and indirect output pathways and a relative dominance of the D1-containing direct pathway may contribute to compulsive behavior (Park, Volkow, Pan, & Du, 2013). While it is not clear at which site this effect is mediated, these findings may be consistent with the role of dopamine receptors in infralimbic PFC in regulating goal-directed actions (Barker,

Torregrossa, & Taylor, 2013), where D2 agonism can restore goal-directed behavior in non-drug exposed animals.

In addition to a potential cortical effect, dopamine signaling within the dorsal striatum has also been shown to be critical for the expression of habitual behavior for psychostimulant rewards (Belin & Everitt, 2008). Functional disconnection of the NAc core-midbrain-DLS circuit (accomplished through unilateral inactivation of the NAc and contralateral dopamine antagonism within the DLS) disrupts stimulus-driven cocaine seeking (Belin & Everitt, 2008). To determine the role of DLS dopamine signaling in ethanol-seeking habits, Corbit and colleagues (2014) infused a dopamine D2 receptor antagonist prior to testing in an outcome-devaluation paradigm. Notably, infusion of the D2 antagonist restored sensitivity to outcome devaluation, highlighting that ethanol, as other reinforcers, is highly dependent on DLS dopamine signaling. The hypothesis that DLS dopamine release is critical to the maintenance of habitual reward seeking is supported by evidence of dopamine transients, or brief dopamine release events, in the DLS to reward cues after extended training. In rats self-administering cocaine, dopamine transients were observed immediately after a reinforced lever press in the NAc early in training, and these signals persisted, albeit at a smaller amplitude, over 3 weeks (Willuhn, Burgeno, Everitt, & Phillips, 2012). In contrast, dopamine transients in the DLS were not apparent in the first week, but emerged with extended training. Similar data were obtained by Shnitko and Robinson (2015) in well-trained rats self-administering sweetened alcohol or sucrose on a variable-interval schedule of reinforcement. Dopamine transients were time-locked to reinforced lever presses in the DLS and NAc, but not the DMS. Interestingly, DLS dopamine release was similar in rats self-administering sweetened alcohol or sucrose, suggesting that these reinforcement-associated dopamine transients in the DLS reflect aspects of instrumental behavior rather than alcohol reward *per se*.

People with a history of alcohol-use disorders exhibit greater activity of the sensorimotor putamen (analogous to DLS in rodents) and use of stimulus-response strategies during instrumental learning as compared to matched controls (Sjoerds et al., 2013). While the effects of alcohol dependence on habit itself have not yet been reported in animal models, chronic alcohol exposure has been shown to alter DLS plasticity and the expression of other DLS-dependent behaviors (Depoy et al., 2013). In this study, Pavlovian-to-instrumental transfer (a task that measures the ability of reward-paired cues to invigorate instrumental responding) was reduced after chronic ethanol exposure. This indicates that the effects of ethanol exposure on stimulus-driven reward-seeking behaviors may be dependent upon the precise ethanol-exposure procedures and behavioral paradigms used.

Corticostriatal circuits and response-strategy selection

In addition to the unique contributions of striatal subregions to the expression of goal-directed actions and habitual behaviors, cortical structures that project to the striatum are critical in the regulation of reward-seeking behavior. A majority of work pointing to cortical control of habitual behavior has implicated structures within the medial PFC, including the infralimbic and prelimbic subregions. The prelimbic PFC sends glutamatergic projections to the NAc core and DMS, as well as additional subcortical structures. This more dorsal

subregion of the medial PFC is necessary for the acquisition of goal-directed actions – lesions or inactivation of the prelimbic PFC prior to training produces premature expression of habitual reward seeking (Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Killcross & Coutureau, 2003). Inactivation of prelimbic PFC does not acutely impair previously learned goal-directed actions (Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009), suggesting that while prelimbic PFC is required for the acquisition of goal-directed actions, it is not critical for their expression.

The infralimbic PFC sends extensive ipsilateral projections to the NAc shell as well as the amygdala and is critical for the expression of habitual reward seeking. Lesioning infralimbic PFC prior to extended training appears to prevent the development (or expression) of habitual reward seeking (Killcross & Coutureau, 2003) and inactivation of this structure can restore goal-directed actions after they have been acquired (Coutureau & Killcross, 2003). As with the striatum, dopaminergic signaling within this structure appears to be critical for response strategy selection, because infusion of dopamine into infralimbic PFC restores goal-directed actions (Hitchcott, Quinn, & Taylor, 2007) that appear to be mediated by dopamine D2-like receptors (Barker et al., 2013). Notably, chronic intermittent ethanol exposure can impair D2/D4 receptor signaling within the infralimbic PFC, resulting in behavioral inflexibility in a set-shifting task (Trantham-Davidson et al., 2014). Though it has not yet been assessed, it is possible that alterations in ventromedial PFC dopamine signaling similarly impair the expression of goal-directed actions after chronic ethanol exposure. While these structures send extensive projections to striatal targets, and their interactions with the ventral striatum have been shown to be critical for reward-seeking behaviors, to our knowledge the role for direct interaction between infralimbic and prelimbic PFC and striatal targets in habitual reward seeking has not yet been determined.

The role of orbitofrontal cortex (OFC) in goal-directed and habitual behaviors has gained significant interest. As with prelimbic and infralimbic PFC, the OFC sends projections to targets within the striatum, including the ventrolateral portion of the striatum and the dorsomedial striatum. In primate models, both the lateral and medial OFC have been implicated in tasks related to behavioral flexibility, including processing outcome value and action-outcome contingencies in the medial OFC (e.g., Roberts, 2006) as well as credit assignment and reversal learning in the lateral OFC (c.f., Noonan, Kolling, Walton, & Rushworth, 2012). Reports investigating the role of these structures in habitual behavior suggest that lesions to the medial OFC do not impact sensitivity to outcome devaluation, indicating that goal-directed action is not dependent upon mOFC activity (Gourley, Lee, Howell, Pittenger, & Taylor, 2010). In contrast, lesions and chemogenetic inactivation to the lateral OFC impair sensitivity to change in outcome value, while optogenetic activation selectively increased goal-directed actions (Gremel & Costa, 2013). In addition, disconnection of the ventrolateral portion of the OFC from its target in the ventrolateral striatum also results in a loss of sensitivity to changes in action-outcome contingencies (Gourley et al., 2013). Together, these data suggest that the lateral OFC, and the interaction between OFC and ventrolateral striatum, are critical for flexible, goal-directed actions.

To gain a greater understanding of how the OFC interacts with striatal targets to drive the expression of goal-directed behaviors, Gremel and Costa (2013) investigated neuronal

activity of OFC and striatal targets in the same animal during instrumental habitual and goal-directed actions. These investigators trained the same mice on distinct schedules of reinforcement (random-interval versus random-ratio schedules) to engender both habitual and goal-directed actions, thereby allowing comparison of the same neurons during habitual versus goal-directed behavior. It was observed that activity of the same OFC and DMS neuron during outcome revaluation tests of goal-directedness were predictive of behavioral outcome – in other words, greater differences in neural activity in these structures were predictive of increased goal-directed action, but were not predictive of habitual actions. This suggests that modulation of activity within this OFC-striatal network may be critical for the expression of flexible, goal-directed behavior. It will be of interest to determine whether these findings obtained with food-restricted mice working to obtain food or a sweet taste will be similar with ethanol-reinforced behavior in the absence of food restriction.

Ethanol effects on corticostriatal function and the development of treatment strategies

Recent research has identified a number of conditions under which ethanol exposure can alter behavioral flexibility. Habit models have shown that ethanol-seeking habits may develop more rapidly than those for non-drug rewards in animals that are self-administering ethanol (Corbit et al., 2012; Dickinson et al., 2002). Importantly, while animals self-administer pharmacologically relevant doses in recent studies of habitual ethanol seeking (0.4–2.0 g ethanol per kg body weight, varying by study), these doses are not likely to be sufficient to engender dependence. However, relatively low doses of ethanol are sufficient to facilitate habitual sucrose seeking as well (Corbit et al., 2012), suggesting that low doses of ethanol may produce general impairments in behavioral flexibility. Few, if any, studies of habitual ethanol seeking have reported blood ethanol concentrations achieved during self-administration. This information is likely to be crucial for understanding the precise effects of ethanol exposure on the development of habitual behavior. While the effects of chronic, high levels of ethanol or binge-like ethanol consumption on habitual behavior have not yet been reported, a number of studies have identified ethanol-induced alterations in behavioral flexibility that appear to be mediated by dysregulation of corticostriatal circuits (DePoy et al., 2013; Depoy et al., 2014). The majority of studies using the outcome devaluation task to study habitual control of alcohol seeking have used the specific-satiety method to devalue alcohol at test. This raises the possibility that acute intoxication might somehow promote habitual responding. One could argue that intoxication rather than altered representation of value suppresses responding for alcohol early in training but no longer does so after extended training, perhaps due to tolerance. The same would not be true, however, for animals that drink alcohol in the home cage but learn to self-administer sucrose. These animals show the same time course for the development of habitual control as animals self-administering alcohol but, importantly, as these animals are satiated on sucrose in the devaluation test, they are not acutely intoxicated. Thus while acute alcohol undoubtedly affects striatal activity (e.g. Yin et al., 2007), it seems more likely that adaptations as a consequence of long-term exposure to alcohol are responsible for the shift in behavioural and neural control (e.g., Wang et al., 2010). The conditioned taste aversion method of devaluation provides an alternative means for manipulating the value of alcohol and is typically conditioned over several days prior to testing. Therefore, animals do not consume alcohol and, thus, are not intoxicated on the test day. This method can be used where the

impact of the acute effects of alcohol is a concern for interpreting results. Of note, where this method has been used, results support the same general conclusion that alcohol promotes more rapid habit formation than rewards such as food (Dickinson, Wood & Smith, 2002).

Unlike the clear relationship between psyschostimulants and dopamine signaling, ethanol exposure has profound effects on multiple neurotransmitter and neuromodulator systems (for review, see Barker & Taylor, 2014). Of particular relevance to this symposium, which highlighted work investigating the mechanisms by which ethanol acts on corticostriatal circuits to alter response strategy selection, alcohol significantly alters glutamate and dopamine signaling. Ethanol is well known to increase dopamine concentrations in dorsal and ventral striatum, as well as the medial PFC (Imperato & Di Chiara, 1986; Robinson, Howard, McConnell, Gonzales, & Wightman, 2009; Schier, Dilly, & Gonzales, 2013; Yim, Schallert, Randall, Bungay, & Gonzales, 1997). In addition, chronic ethanol exposure alters dopamine receptor signaling in the ventromedial PFC (Trantham-Davidson et al., 2014) such that D2/D4 (but not D1) signaling is impaired. This observation appears to be consistent with the identified role of infralimbic D2-like signaling in the expression of goal-directed sucrose seeking. Alcohol also inhibits activity within PFC neurons in a dopamine-dependent manner (Tu et al., 2007) that likely impacts subsequent glutamatergic signaling in subcortical projection targets. Indeed, both acute and chronic ethanol exposure impact glutamate signaling within corticostriatal circuits. Acutely, ethanol inhibits NMDA receptor function in both the cortex and subcortical targets including the striatum (Woodward, 2000; Yin, Park, Adermark, & Lovinger, 2007), and repeated ethanol exposure has been shown to produce sensitized glutamate release in the NAc (Szumlinski et al., 2007). Chronic ethanol exposure results in increases in extracellular glutamate in the NAc (Griffin, Haun, Hazelbaker, Ramachandra, & Becker, 2013), as well as alterations in both metabotropic and ionotropic glutamate receptor expression that could be related to the expression of behavioral inflexibility (Kroener et al., 2012; Meinhardt et al., 2013). While dopamine and glutamate signaling in the dorsolateral striatum have been directly implicated in the expression of habitual ethanol seeking (Corbit et al., 2014; Shnitko & Robinson, 2015), and while the normal functioning of these systems is likely to be altered by chronic exposure to alcohol, the precise mechanisms through which alcohol exposure impacts these signaling pathways in regions responsible for goal-directed and habitual behaviors to ultimately facilitate the acquisition and expression of habitual reward seeking, remain to be elucidated.

Data suggest that ethanol exposure acts not only to alter the corticostriatal circuitry that underlies the transition from action and habit, but also that ethanol-paired cues can both promote ethanol seeking (e.g., Barker, Torregrossa, & Taylor, 2012; Corbit & Janak, 2007) and independently impair the ability to perform goal-directed behavior (Ostlund et al., 2010). With this in mind, ongoing work is exploring behavioral and pharmacological means for improving extinction of ethanol-related stimuli with the aim of reducing their impact on behavior (Leung & Corbit, unpublished).

The studies presented in this symposium generally use animal models of instrumental behavior in which goal-directed and habitual behaviors are operationally defined to be distinct and therefore can be independently measured. These behavioral paradigms appear to

have good construct validity for modeling the human condition. Indeed, homologous structures have been implicated in the expression of habitual behavior in humans as in rodents (Balleine & O'Doherty, 2010; Tricomi, Balleine, & O'Doherty, 2009).

While habitual alcohol seeking models only one component of addictive behavior, we believe that a greater understanding of ethanol's effects on the neuroanatomical substrates of habitual behavior will lead to the development of novel pharmacotherapeutic and behavioral strategies for the reduction of alcohol-seeking behavior. For example, one prediction is that drugs such as naltrexone that pharmacologically reduce alcohol reward or craving (O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002) might be less effective in heavy drinkers with strong habitual drinking strategies. Indeed, Hay and colleagues (Hay et al., 2013) found that naltrexone was less effective in reducing self-administration and cue-induced reinstatement of alcohol seeking in rats that were trained on habit-promoting reinforcement schedules as compared to goal-directed rats. By increasing the ability to regulate alcohol-seeking behaviors, we expect future manipulations will enable greater self-control in individuals, thereby preventing initiation and relapse of cue-elicited drinking.

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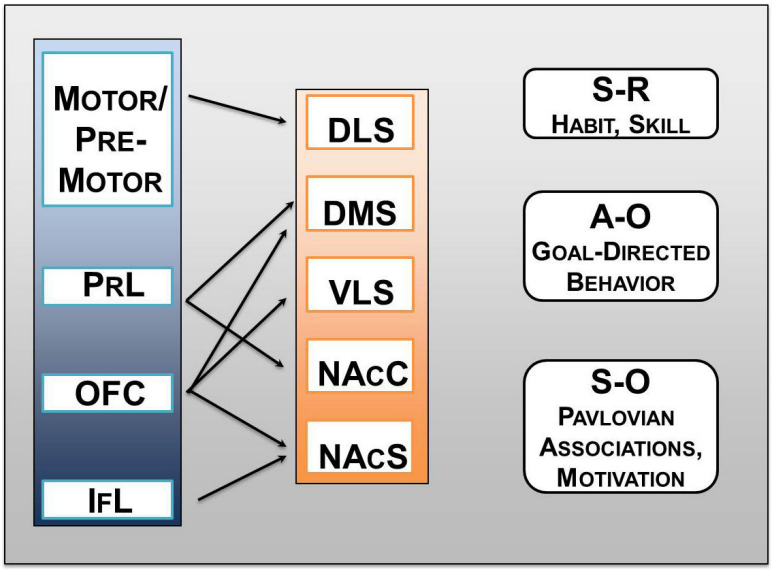

Fig. 1.

Corticostriatal circuits in the regulation of response strategy selection. Cortical structures extensively innervate the striatum with a gradient in topographic projections. More ventral regions of the medial PFC predominantly project to the more ventral regions of the striatum – critical for stimulus-outcome associations, motivation, and potentially integrating information to drive goal-directed actions. More dorsal PFC structures largely project to more dorsal subregions of the striatum. In particular, prelimbic PFC projects to ventral striatum regions, as well as the dorsomedial striatum which is critical for goal-directed actions. Sensorimotor cortices, in contrast, send significant projections to the dorsolateral striatum, critical for the performance of stimulus-response habits. *PrL: prelimbic prefrontal cortex; OFC: orbitofrontal cortex; IfL: infralimbic prefrontal cortex; DLS: dorsolateral striatum; DMS: dorsomedial striatum; VLS: ventrolateral striatum; NAcC: nucleus accumbens core; NAcS: nucleus accumbens shell; S-R: stimulus response; A-O: action-outcome; S-O: stimulus-outcome*.