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Translational Research on Habit and Alcohol

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Abstract

Habitual actions enable efficient daily living, but they can also contribute to pathological behaviors that resistant change, such as alcoholism. Habitual behaviors are learned actions that appear goal-directed but are in fact no longer under the control of the action's outcome. Instead, these actions are triggered by stimuli, which may be exogenous or interoceptive, discrete or contextual. A major hallmark characteristic of alcoholism is continued alcohol use despite serious negative consequences. In essence, although the outcome of alcohol seeking and drinking is dramatically devalued, these actions persist, often triggered by environmental cues associated with alcohol use. Thus, alcoholism meets the definition of an initially goal-directed behavior that converts to a habit-based process. Habit and alcohol have been well investigated in rodent models, with comparatively less research in non-human primates and people. This review focuses on translational research on habit and alcohol with an emphasis on cross-species methodology and neural circuitry.

Keywords

alcohol use disorders; dopamine; executive function; animal model; addiction; goal-directed; putamen; caudate; dorsolateral striatum; dorsomedial striatum; stimulus-response

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Human and Animal Rights and Informed Consent

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Conflict of Interest

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Introduction

Stimulus response (S-R) learning is a highly adaptive faculty that allows us to more efficiently navigate our world. Cognitive flexibility, in turn, enables us to override these learned, habitual responses in favor of new, goal-directed responses when action-outcome contingencies change. Normal learning processes involve the formation of circuits through which stimuli can come to drive actions [1]. Such S-R actions are habit-based, rather than goal-directed; this enables efficient response selection, which frees up cognitive resources. However, habit-based actions are controlled by triggering stimuli instead of by the action's outcome. Consequently, suppressing these actions can prove difficult, which can lead to persistent maladaptive actions if the outcome of these actions turns negative. Goal-directed and habitual behaviors appear to rely on distinct but parallel frontostriatal circuits, according to several lines of data [2–6]. For example, both animal and patient lesion data implicate frontostriatal circuits in the transition from goal-directed to S-R behaviors [7–12]. Moreover, rodent studies demonstrate the dominance of distinct connections between the rodent medial prefrontal cortex (homolog of the primate dorsolateral prefrontal cortex) [13] and particular striatal sub-regions during goal-directed versus habitual actions [11, 12, 14–23]. Primate studies and human neuroimaging studies complement these findings by implicating the dorsolateral prefrontal cortex in the goal-directed formation of novel S-R associations, and the dorsolateral striatum (putamen) in mediating habitual behaviors [24–36].

Alcoholism is a chronic, relapsing disorder in which affected individuals tend to cycle between sustained periods of compulsive drinking and periods of abstinence. Such relapse despite serious negative consequences is a particularly pernicious aspect of alcohol use disorders (AUDs) [37]. This insensitivity to drinking consequences likely reflects, in part, maladaptive associative learning following chronic alcohol misuse [38–40]. The transition to a condition in which alcohol consumption no longer yields solely rewarding outcomes, but also negative outcomes, resembles reward devaluation procedures used in animal models of habit, for example when consumption of a reward is paired with a sickening lithium chloride injection [41]. The complexity in the characteristics and etiology of AUDs preclude drawing the simplistic conclusion that such disorders solely reflect a transition from goal-directed seeking of alcohol reward or relief, but a variety of evidence supports the idea that such processes may contribute to AUDs, perhaps due in part to the effects of ethanol, particularly chronic ethanol, on action-selection circuitry.

Alcohol-directed behaviors recruit and engage similar neural circuitry to that engaged during other learning and memory processes [42]; however, alcohol's reinforcing properties are thought to strengthen the representation of behaviors associated with alcohol use and to strengthen the association of these behaviors with alcohol cues. Thus, alcohol-associated stimuli may be potent triggers of S-R behaviors, even in the absence of alcohol, potentially leading to relapse. This issue is compounded by the fact that chronic alcohol misuse may potentiate the activation of circuits encoding habitual actions and alter associative learning processes [43, 44]. Understanding the role of S-R circuits in the development of AUDs may provide insight into the predicted effectiveness of different treatment options.

Here we endeavor to draw parallels between the habit and alcohol research in animal models and humans, and to emphasize difficulties in translation and current gaps in our knowledge. This review is not intended to be an exhaustive review of the extensive literature linking alcohol and habit, but rather to provide an up-to-date summary on research in this area with an emphasis on cross species comparisons, from *in vivo* and *in vitro* work in rodent and primate models to work in human subjects.

Assessing Action Selection Strategies

Animal models of habit

Decades of research have yielded behavioral models that can assess the development and expression of habitual behaviors in rodents and non-human primates, which we briefly describe here. Habitual behavior in animal models is typically studied in the context of instrumental or operant behaviors. One straightforward way to promote habitual behavior is to *overtrain* animals – that is, prolonged training such that the operant response becomes automatic. Overtraining is often used to study habitual behavior in non-human primates [45–49] and used less often in rodents [1, 14]. Monkeys are trained to execute automatic actions through a long-term learning period including thousands of action-outcome pairings [for example, see 50]. In this type of learning, the latency of action initiation and the number of errors gradually decrease [for review, see 51, 52], and the automatic action is usually triggered by a context or stimulus associated with a reward.

Another experimental strategy is to employ reinforcement schedules that promote habit-like reward seeking. The *random or variable interval schedules of reinforcement* are based on a low perceived response-reward contingency, as an operant response produces a reward only after a variable time-interval elapses [e.g. 1, 53, 54–57]. Under random or variable interval reinforcement schedules, performance is less dependent on predictable reward delivery, and thus operant responding persists longer under extinction conditions or contingency changes. This action persistence despite changing contingencies or outcome value defines habitual actions. *Second-order or chained schedules of reinforcement* can also produce habitual drug or reward seeking in both non-human primates and rodents [58–64]. Typically, after animals are trained to make an operant response for a reward, they next learn to make the operant response to obtain a conditioned stimulus (CS) associated with the reward. Operant responding for the CS maintains the behavioral response with only occasional actual reward deliveries.

How do we know when an animal employs a habitual strategy? Dickinson and colleagues described two main methods for assessing habits in rodents that have been adopted by the scientific field: *reward devaluation* and *degradation of the action-outcome contingency* [41, 65]. If an animal adjusts its operant behavior to compensate for the different circumstances employed by either method, the animal's action is considered goal-directed; if the behavior is maintained despite change in reward value or contingency, the animal's action is considered to be habitual. Devaluation of the primary reinforcer is often achieved via pairing reward consumption with lithium chloride administration to produce a conditioned taste aversion. A less permanent devaluation is attained with a specific-satiety procedure, in which an animal is given free access to the reward prior to the test session and allowed to

“consume to satiety.” In both approaches, the flexibility of the reward-seeking behavior is assessed in extinction conditions – i.e. without feedback from the devalued reward – and similar operant responding under the devalued and valued reward conditions is interpreted as habitual behavior. Assessment in extinction is important, because when the animal experiences the devalued reward, operant behavior for that reward declines, even when reward seeking previously appeared to be a habitual action. This type of assessment is widely used in rodents [e.g. 20, 41, 57, 66] and in non-human primates [46, 67]. Degradation of the response-reward contingency can be achieved either by using an omission reinforcement schedule (e.g., reward is delivered only when an operant response is withheld) or by simply removing the action-outcome contingency and providing “free” rewards irrespective of the animal’s operant behavior. These tests measure the flexibility of an animal’s reward-seeking behavior – with inflexibility termed “habit” – although it is noteworthy that only the operant behavior and not the reward consumption is assessed. In other words, it is not clear that the eating or drinking of the reward is actually a habitual, S-R action.

Paradigms to assay habit in humans

As described above, various experimental paradigms can yield habitual responding in animal models. Translating these paradigms to select human subject populations has met with limited success, as it is hard to test habits *per se* in people. As a result, human studies typically evaluate S-R action strategies as a proxy measure of habit, but while habits are S-R strategies, not all S-R actions are habitual.

Major constraints in translating paradigms to humans are the length of training/repetition required to achieve overtraining, and the selection of stimuli and reward outcomes used to elicit behavioral response selection. For human subjects, the most common reinforcer is monetary reward, or an abstract “points” system, both of which are very difficult to devalue. Essentially, earning money or scoring points is always intrinsically valuable to people. Some human studies have directly imitated animal specific-satiety methods, but a major limitation is that participants are restricted to those who like these specific food or drink options (e.g. tomato juice, Fritos, or chocolate) [35, 36, 68]. This poses a particular problem when studying special populations, such as people with AUDs, who are harder to recruit in general, and can result in substantial selection bias. Additionally, prior experience with specific food or drink rewards, either in the lab or in the “real world,” could impact choice behavior during devaluation. To avoid the use of actual food outcomes, an alternate approach has used food pictures to test goal-directed and habitual responding to these pictures following training [4, 34, 69]. A limitation of this method is that the pre-existing familiarity of these images may vary substantially between individuals, potentially interfering with training effects. As such, confounds associated with these approaches may yield individual differences in behavior that either mimic or preclude detection of manipulation effects in human studies.

To avoid food reward devaluation through specific-satiety procedures, some scientists have manipulated reward outcome value via instructed devaluation. The use of food rewards *without the opportunity to actually consume the food* has face validity with assessments of

habit in animal models that use reward devaluation and test in extinction. deWit et al (2007) has developed a “fruit task” in which fruit pictures serve as both stimuli and outcomes (in different trials) and correct responses earn points [4]. This paradigm includes congruent and incongruent trials during associative learning, favoring either goal-directed or habit-based response strategies to maximize performance and winnings. In the congruent condition, each fruit picture is paired with a single response type. In the incongruent condition, when an image is a stimulus, it’s associated with one response, but when the same image is an outcome, it’s associated with a different response, which creates response conflict. Outcome devaluation is accomplished by instructing participants that responding to certain (devalued) fruit images no longer gains points. To optimize task performance in the incongruent condition, responses should be based on S-R associations, which do not include the consequent outcome and are thus insensitive to outcome devaluation. In contrast, both S-R and goal-directed strategies can maximize points earned in the congruent condition. This fruit task has been combined with a test to measure ‘slips of action’ [70]. The goal of this behavioral measure of instructed devaluation is to quantify the relative goal-directedness versus habitual nature of actions. Responding to a devalued outcome (a ‘slip of action’) results in loss of points and are expected to occur if S-R associations dominate during instrumental learning. Again, pre-existing interferences from experience outside of the lab setting could result in changes in reward value and diminish the effects of devaluation that are aimed at manipulating outcome value for study rewards.

To avoid the confounds detailed above, another approach is to use novel, abstract visual stimuli in human studies. Studies of S-R learning in humans have taken this approach, employing one-to-one mapping of a few stimuli onto an equal number of response keys [27, 71]. Typically these tasks have used two keys, and since humans are able to learn these associations very quickly, they can be used to study an established S-R strategy, but their utility in examining learning over time for the time frame of neuroimaging studies is not ideal. The temporal effects of repeated training to induce habitual responding do not always mimic animal studies, and so matching goal-directed versus habitual behavior on the same time scale as animal instrumental training is not always feasible. To transcend these limitations, Boettiger & D’Esposito conducted an fMRI study of S-R learning [33] with a task with cross-session stability in neural activations and that allows for a large number of permutations, which enables repeated task use without confounding practice effects. In this task, participants learn by trial and error to associate sets of abstract visual stimuli with specific manual responses. Participants complete an initial training session, followed by a second testing session, making study sessions reasonable for a laboratory context. Notably, this paradigm also incorporates a “response-devaluation” manipulation that changes S-R contingencies to assess habitual responding. This novel manipulation allows a direct comparison between the ability of participants to change well-established versus newly acquired contingencies to investigate both S-R acquisition and persistence of established S-R actions. The timescale of the transition between goal-directed and habit-based responding is currently unresolved, and represents an important avenue of future human research.

Another alternative approach that is frequently employed in human subjects is the use of probabilistic learning tasks [72]. The paradigm that incorporates this framework utilizes a probabilistic, sequential Markov decision task with two sequential choices; the final choice

produces either a reward or no reward outcome. Abstract visual images are displayed at each decision stage, forming a decision tree. During each trial, the first abstract images are presented, and participants must press the left or right button. The first choice stage presents options with fixed outcome probabilities, while the second stage's reward probabilities change slowly and independently in successive trials. In this paradigm, model-free action selection favors repeating S-R associations that yield rewards, while model-based action selection better optimizes rewards using a goal-directed planning to predict reward outcomes. This approach equates model-based strategies with goal-directedness and model-free choices as habit-based [72]. As noted above, however, S-R strategies are not necessarily habitual. Moreover, this sort of paradigm has utility in stretching out the learning over time, but it lacks ecological validity.

The neural and behavioral results from studies using the model-free and model-based computational framework support previous human and animal work on the behavioral and neural correlates of goal-directed and habitual control, but this was not directly tested in relation to the standard devaluation manipulation until recently. Friedel et al. [73] used a within-subject design in healthy participants to test the correspondence of behavioral results from outcome devaluation via sensory-specific satiety and the sequential decision making task. For outcome devaluation, liquid food rewards were consumed to promote a food specific satiety (as per Valentin et al. [35]) and to test whether behavior was goal-directed or habitual; the sequential decision-making task (as per Daw et al. [74]) allowed participants to use either an S-R (model-free) or goal-directed (model-based) strategy, or both, throughout to maximize task earnings. This study demonstrated a positive correlation between goal-directed behavior after devaluation and the use of a model-based strategy in the sequential decision-making task, providing evidence for construct validity of goal-directed behavioral measures across these two forms of tasks. An outstanding question is whether extensive training on these tasks can result in habitual responding and whether this correlates with the use of model-free strategies; the parameters of the sequential decision making task may not as readily test enhanced habitual behavior, necessitating extended training or manipulation of task structure such that the most advantageous strategy to maximize reward is S-R driven.

Neural Circuitry of Habit

Comparative habit circuitry

Studies in rodents and non-human primates have made remarkable progress in mapping the neurocircuitry of S-R behavior [for review 40, 75, 76] (Figure 1). Typical approaches to study the neurocircuitry of action selection are permanent lesions of specific regions done before training or transient, pharmacological inactivation of specific regions after training, followed by assessment of habit as described above. Lesion and inactivation experiments have identified the *dorsolateral striatum* as a key site for habit formation and maintenance in rodents [20, 77, 78]. Further, electrophysiological studies have found distinct firing patterns of neurons in the dorsolateral striatum during habit-like reward seeking as opposed to goal-directed seeking [53, 54]. The primate homolog of the rodent dorsolateral striatum, the *putamen*, plays a similar critical role in habitual or automatic behavior [45, 47–49]. Moreover, numerous studies have indicated involvement of neocortical and allocortical

regions in the establishment and performance of habitual actions. For example, lesion, inactivation and optogenetic inhibition of the *infralimbic area* of the medial prefrontal cortex disrupts S-R behavior in rats [14, 16, 18]. The infralimbic area in rats has strong connections with ventral striatum [especially the nucleus accumbens shell, 79]) and these brain regions are critical in the control of reward-motivated behavior invigorated by reward-associated stimuli [80]. As these stimuli can also trigger habitual behavioral responses, disruption of accumbal glutamatergic innervation from the infralimbic cortex might disrupt habitual performance via lack of appropriate stimulus-associated processing. In contrast, impairment of the *prelimbic area* promotes establishment of inflexible, habitual behavior in rats [16]. This brain area has strong connections with the dorsomedial associative striatum, which is essential for goal-directed behavior. Therefore, lack of prelimbic innervation might promote the transition from goal-directed to habitual behavior. In primates, lesions of the *orbitofrontal cortex* and *dorsal cingulate cortex* promote the establishment of inflexible habitual behavior [17, 46]. Intact functioning of the orbitofrontal and cingulate cortices are important for decision-making based on action-outcome contingency; moreover, their functions are dependent on anatomical connectivity between the cortex and the basolateral amygdala in primates [81]. Therefore, lesion of these cortical areas disrupts goal-directed behavior, thus leading to habitual performance.

The amygdala has been strongly implicated in the development and performance of habitual behavior. A detailed analysis of amygdaloid projections in primates [82, 83] demonstrated evidence of direct projections from the amygdaloid complex to rostral putamen, olfactory tubercle, and orbitofrontal and cingulate cortices [82, 84]; therefore, blocking activity in the amygdala might affect habitual behavior in primates. Indeed, muscimol-induced inactivation of the *basolateral amygdala* disrupts habitual behavior in primates [67]. In contrast, lesion of the basolateral amygdala in rats promotes the transition of goal-directed behavior to habit [85], while lesion of the *central amygdala* disrupts previously formed habits [86]. The basolateral amygdala is a major source of amygdalostratial projections in rats, with massive inputs from the medial basolateral amygdala to the dorsal striatum and from the lateral basolateral amygdala to the ventral striatum [87]. No studies to date have investigated the effect of basolateral amygdala inactivation on formed habits; thus, future investigations might address this. In contrast, the central amygdala modulates activity of the substantia nigra pars compacta and consequent dopaminergic activity in the dorsolateral striatum in rats [88], which may in turn influence habitual behavior.

This body of evidence demonstrates that establishing and executing habitual behavior requires intact functional activity within the dorsolateral striatum, infralimbic cortex and central amygdala in rats and within the putamen and the basolateral amygdala in primates. Thus, these structures form the “habit circuits” in rats and non-human primates (Figure 1). Conversely, the basolateral amygdala and the prelimbic cortex in rats and the orbitofrontal and cingulate cortices in primates form “goal-directed circuits” in rats and non-human primates, and impaired connectivity within these circuits shifts behavioral control toward habitual, S-R strategies.

Habit circuitry in humans

Recent evidence in humans is consistent with the importance of communication between frontostriatal circuits in action selection. Human studies examining goal directed behavior have demonstrated that activity in the orbitofrontal cortex (OFC) is decreased for a devalued response, that ventromedial prefrontal cortex (vmPFC) activity encodes outcome value, and that the dorsolateral prefrontal cortex (DLPFC) is active during S-R learning [33, 35, 89]. In addition, as with the DMS in rodents, the anterior caudate nucleus plays a role in action-outcome contingency [34, 90–92]. Habitual behavior, on the other hand, is associated with activation of the posterior putamen/globus pallidus and decreased vmPFC activation during habitual responding [93, 94]. Computational modeling of human choice behavior has further demonstrated that prefrontal brain regions arbitrate between model-free or model-based response selection in healthy controls [95]. More directly, transcranial magnetic stimulation has been used to induce a transient lesion within the dorsolateral prefrontal cortex, thereby shifting the balance from the use of a goal-directed (model-based) to a habit-based (model-free) response selection strategy [96]. In contrast to these findings, manipulating the right dorsolateral prefrontal cortex through transcranial direct current stimulation does not affect model-free or model-based performance [97]. While transcranial stimulation manipulations are confined to cortical areas, they confirm that cortical activity is critical in action selection strategy. Dopaminergic processes in action selection have also been studied. One approach used is dopamine precursor depletion to transiently lower dopamine synthesis and release. Relative to control conditions, dietary dopamine depletion had no effect on habitual and goal-directed behaviors after outcome devaluation with the de Wit fruit task; in contrast, the slips of action test showed that dopamine depletion resulted in more habitual responding [98]. Finally, enhancement of dopamine by L-DOPA administration in healthy subjects performing the two-step Markov decision task showed that participants demonstrated greater use of a model-based strategy following L-DOPA compared to placebo [99]. Thus, human subject studies are consistent with animal models indicating that dopamine levels, presumably in target regions such as the caudate, putamen, accumbens, prefrontal cortex and amygdala, modulate the choice between goal-directed and habitual action (Figure 1).

Alcohol effects on habit circuitry

Animal models

The pharmacological effects of alcohol and its metabolites on brain mechanisms are complex and depend on a variety of factors such as drinking doses (heavy versus moderate), duration (acute versus chronic), age (adolescence versus adult), drinking patterns (intermittent versus continuous) and withdrawal state (acute or prolonged). In general, acute alcohol has dose-dependent effects that are initially activating and later sedating. Under chronic alcohol exposure, neuroadaptations develop that compensate for the inhibitory effects of the drug, resulting in hyperexcitation upon withdrawal and abstinence. Relevant to habit formation and expression, there is a rich literature describing the acute and chronic effects of alcohol on neurotransmission, synaptic plasticity and morphology of neurons and glia within the brain structures included in the “habit” and “goal-directed” circuits in rats and non-human primates [for review, see 100, 101–104]. Thus, alcohol consumption may disrupt normal functioning of the “goal-directed” circuit and thereby promote habitual

behavior, as well as directly potentiate function in the “habit”-related structures and support maintenance of habitual performance.

Many studies describe acute effects of alcohol on synaptic plasticity, specifically long-term depression (LTD) and long-term potentiation (LTP), within the striatum, cortex and amygdala. For example, LTD in dorsal striatum depends on activation of dopamine type 2 (D2) and cannabinoid type 1 (CB1) receptors, while induction of LTP requires activation of dopamine type 1 (D1), NMDA-type glutamatergic and muscarinic acetylcholine receptors [102]. NMDA receptors are a primary target of ethanol and acute ethanol’s antagonistic effect on NMDA function has been demonstrated in striatum, cortex and amygdala [105–109]. Additionally, acute alcohol might further affect synaptic plasticity in the striatum by enhancing tonic and phasic dopamine release [for example see 110, 111] which would activate D2 and D1 receptors, or by acting on CB1 receptors [112].

Chronic alcohol effects on striatal circuitry and neuronal activity have been extensively investigated [104, 113–115]. For example, long-term alcohol consumption depresses GABA neurotransmission and enhances excitability of the medium spiny neurons in both the primate putamen [116] and the dorsolateral and dorsomedial striatum of mice [117]. In addition, chronic alcohol exposure increases spine density on the medium spiny neurons in the putamen [116]. Moreover, long-term alcohol intake induces neurochemical adaptations in the dorsolateral caudate of primates, including increased sensitivity at kappa opioid receptors and reduced dopamine release and clearance [118], although the role of this subregion of the dorsal striatum in habit strategies is unclear. In rats, chronic intermittent alcohol exposure attenuates the induction of corticostriatal LTD in dorsolateral striatum by acting on extracellular signal-regulated kinase pathway or decreasing endocannabinoid signaling [119, 120]. Likewise, the effects of ethanol exposure on neuronal activity in the amygdala are well described [121–123]. For example, chronic alcohol exposure increases glutamatergic synaptic transmission in the amygdala of rats by upregulating kainite- and AMPA-type glutamate receptors [124, 125], decreases presynaptic GABAergic functioning, alters the expression of GABA_A receptor subunits, and decreases corticotropin releasing factor mRNA [126–128]. Finally, the prefrontal cortex is also affected by chronic alcohol exposure. For example, in the medial prefrontal cortex of rats, chronic alcohol exposure increases spine density of pyramidal neurons, reduces expression of myelin basic protein and number of glia, and disrupts signaling through dopamine D2 and D4 receptors [129–131]. Prefrontal cortical regions also exhibit enhanced innate neuroimmune gene expression after chronic ethanol [132] and blunted neural responses to alcohol challenge [133], especially when exposure occurred in adolescence. In non-human primates, chronic alcohol self-administration results in smaller volumes of frontal areas and alters both GABAergic and glutamatergic transmission in the dorsolateral prefrontal and orbitofrontal cortices by decreasing GABA_A and NMDA receptors [134–136]. Thus, chronic alcohol intoxication leads to significant alterations within the corticostriatal circuits and amygdala, brain structures involved in the formation and maintenance of habit-based actions, consistent with the hypothesis that heavy alcohol drinking promotes a loss of behavioral flexibility and a reliance on habit-based action-selection strategies.

Humans

Investigation of the neural effects on brain circuitry associated with habitual responding is dramatically more limited. The effects of both acute and chronic alcohol exposure on the human brain more broadly has been recently and exhaustively reviewed [137, 138]. In keeping with data from the animal literature, acute alcohol administration affects brain structures implicated in motivation and behavior control, i.e. in regulation of automatic and goal-directed actions. Furthermore, chronic alcohol intoxication correlates with structural and functional abnormalities in these same structures [137]. We do know that acute ethanol induces release of dopamine in the striatum, albeit with considerable variability across subjects in the spatial distribution of such release [139]. In addition, acute alcohol induces release of endogenous mu-opioid ligands in the orbitofrontal cortex of humans [140]. Also consistent with the animal literature, postmortem human brains show a correlation between lifetime alcohol use and neuroimmune signaling in the prefrontal cortex [141]. Together, the available data support the view that acute and chronic effects of ethanol on habit-related circuitry are largely consonant across species.

Alcohol effects on habitual behavior

Alcohol drinking is initiated at different ages and for variety of reasons. Drinking initiation is often considered to be a goal-directed behavior targeting a variety of primary aims, such as facilitating social interaction, feeling drug-induced euphoria, or coping with stress, anxiety or depression [142, 143]. However, animal studies demonstrate that chronic or persistent alcohol drinking, sometimes even at small doses, can develop into inflexible habitual alcohol seeking [53, 57, 144]. Once formed, habits are hard to break; therefore, the transition from occasional goal-directed to habitual alcohol seeking, and perhaps drinking, is an important aspect in our understanding the development of AUDs [145]. Note that whether the habit extends to alcohol drinking is less understood, as animal models of habit are based on assessment of the operant behavior (seeking) and not the actual consumption (drinking).

Data from rodent models

Major progress in the investigation of goal-directed versus habit-like alcohol seeking behavior has been made with rodent models and is the subject of several recent reviews [145–147]. Early studies of whether alcohol could support or even promote habitual operant behavior were inconclusive [148, 149]. More recently, using a random-interval schedule of reinforcement, Corbit and colleagues (2012) showed that alcohol drinking in rats became habitual over 4–8 weeks of training, while sucrose did not promote habit in this time period [57]. In Corbit's study, rats were acclimated to drink a 10% ethanol solution in their home-cages prior to self-administration training, and similar home-cage alcohol exposure also promoted habitual seeking of sucrose [57]. In another study, mice chronically exposed to ethanol vapor and then trained to operantly self-administer ethanol were insensitive to ethanol devaluation compared to mice without the previous exposure [150]. Other studies have reported habitual alcohol seeking, but either did not compare ethanol to sucrose self-administration [53] or did not detect differences [55, 56]; however, these studies did not include a prior ethanol exposure period, but only ethanol self-administered in the operant

chamber. Taken together, these studies demonstrate that alcohol self-administration can transition from a goal-directed to a habitual behavior in rodents, and that a history of alcohol exposure can promote the speed of this transition.

Data from non-human primate models

Overall, there is less behavioral evidence obtained in non-human primates addressing alcohol effects on the transition from goal-directed behavior to habit, although alcohol appears to support habit-like behavior. In baboons trained to self-administer 4% ethanol under a 3-component chained schedule of reinforcement, ethanol-seeking behavior persisted even under extinction conditions (i.e., only reinforced with ethanol-associated cues, but no longer with ethanol), while water-seeking behavior extinguished [62]. While “habit” was not directly tested, these findings demonstrate that alcohol seeking can be insensitive to reward omission and can be triggered by reward-associated cues, similar to a habitual behavior. Additionally, Cuzon Carlson and colleagues (2011) demonstrated in cynomolgus monkeys that long-term alcohol intake (22-hour daily access over more than two years) induces a habit-like, inflexible pattern of drinking behavior controlled by the environmental context [116].

Alcohol effects on habitual behavior in humans

Despite the growing body of literature on habitual behavior in humans, there are a limited number of studies examining the relationship between acute or chronic effects of alcohol on habitual responding. As described below, results from the most recent studies in humans generally indicate reduced behavioral flexibility associated with AUDs, but there remains a need for future work to expand our knowledge on the both the behavioral and neural circuitry of habitual behaviors in AUDs.

A laboratory study to test the effects of acute alcohol administration on response selection used a two-choice reward paradigm in which participants could earn points toward earning chocolate or water [151]. Participants consumed either an alcoholic beverage or placebo beverage prior to the choice task, in which they selected keys to earn hypothetical chocolate or water “points” with a reward probability of 50%. To assess action-selection strategy, satiety (consumption of 3 bars of chocolate) was used to devalue the chocolate reward; participants were then tested for choice behavior for water and chocolate “points” under extinction conditions in which no choice outcome feedback was provided. Alcohol administration prior to the choice task reduced goal-directed control of chocolate selection. Specifically, chocolate selection was insensitive to devaluation and participants continued to respond for this devalued outcome [151]. Thus, this study supports the notion that acute alcohol potentiates habitual action.

A recent neuroimaging study by Sjoerds et al. [93] examined the effects of chronic alcohol use on habit-based responding in alcohol-dependent patients using the fruit task described above. In that study, alcohol-dependent individuals demonstrated habitual responding at the expense of goal-directed choice selection in comparison to controls. Interestingly, the authors mention that a version of the task in which fruit pictures were substituted with alcohol pictures was also used, but that picture type did not impact either behavior or

neuroimaging results. Neuroimaging results from this study include greater activation of the posterior putamen and less activation of ventromedial prefrontal cortex during instrumental learning and choice behavior in the alcohol-dependent group relative to controls. In contrast, healthy controls showed greater ventromedial prefrontal cortex and anterior putamen activity during action selection in goal-directed trials relative to the alcohol-dependent group. For incongruent trials, response selection was associated with posterior putamen and dorsal caudate nucleus activation, and the alcohol-dependent group demonstrated greater activity in the posterior putamen relative to controls. This was the first study to report neural correlates of preferential habit-based responding in AUDs; however, attributing the study outcome solely to AUD status is complicated by the fact that the participants were using psychoactive medications for comorbid anxiety and depression.

In another study, the use of a computational framework for decision-making was used to measure choice behavior in recently detoxified, alcohol-dependent individuals [152]. Participants completed a 2-stage Markov decision task to quantify model-based (goal-directed) or model-free (habitual) responding. In contrast to Sjoerds et al. [93], Sebold et al. [152] found that the alcohol-dependent group did not show stronger model-free (habitual) behavior. However, healthy controls employed model-based strategies more than the alcohol-dependent group did. Specifically, healthy controls were more sensitive to transition frequency after losses and, therefore, used a model-based strategy. In contrast, the alcohol-dependent group was unable to utilize goal-directed control after non-rewarded trials to maximize task performance, indicating reduced flexibility. Differences between the behavioral findings of these two studies may reflect differences in the sample characteristics, including those noted above, as well as differences in task, and in abstinence duration and therefore withdrawal state.

Conclusion

Together, the available evidence generally supports the conclusion that across rodents and primates, largely homologous brain circuits contribute to the regulation of automatic versus goal-directed actions. Moreover, available evidence suggests universal sensitivity of this circuitry to acute and chronic ethanol exposure, although a thorough understanding of the precise effects of such exposure is not yet complete and remains most fully investigated in rodents. Consistent with these neural findings, chronic ethanol appears to promote habitual over goal-directed action-selection in both rodents and primates, although, again, this phenomenon remains to be fully explored. One area where the primate and rodent literature diverge is in terms of evidence for the relative importance of the amygdala. Non-human primate data tends to support a role for different subregions of the amygdala for generating habit-based versus goal-directed responses, but such evidence in rodents is lacking. It remains to be seen what role the amygdala may play in human subjects, but the advent of ultra high-resolution neuroimaging in humans may enable thorough investigation of this issue.

A limitation of current animal models of habit is that assessments occur under extinction conditions and there is little evidence that manipulations that reduce habitual strategies of alcohol seeking actually reduce alcohol consumption. Indeed, in an operantly trained rat, one

would not expect that disruption of neural processing in habit circuits would necessarily disrupt alcohol self-administration, because other corticostriatal regions would maintain the behavior – only the flexibility of that behavior would change [40]. Nevertheless, a change from inflexible to flexible alcohol drinking may have important consequences, such as less susceptibility to relapse and sensitivity to negative consequences. In addition, it is possible that manipulations in the habit-controlling regions may reduce excessive drinking, as indicated by a recent case study in which an ischemic event in the left caudate-putamen resulted in cessation of daily, heavy alcohol and nicotine use [153].

The main challenges for translation in the area of alcohol and habit arise from the inherent differences between humans and other animals. First, effective reward schemes differ for humans and other animals, which limits the utility of most operant paradigms employed for habit research in animal models. Moreover, the animal habit literature to date has focused exclusively on reward-seeking behaviors, while human data show that learning actions that enable avoidance of aversive states may also transition from goal-directed to habit-based [154]. This is particularly important in light of the considerable evidence that along with a transition from goal-directed reward-seeking to habitual drinking, that there is also a transition from drinking for alcohol's positive effects to drinking to relieve aversive states [155]. Understanding how these two transitions may interact to promote AUDs is an important future avenue of research. Second, the tools for neural investigation differ dramatically between humans and other animals. Whereas human neuroimaging methods enable more or less whole-brain investigation of ongoing neural activity, the duration of functional scan sessions is limited to approximately one hour. The constraints on the measured signal limit the temporal resolution to about 0.5 second and require numerous repetitions of the same condition to overcome inherent noise in the system. This stands in stark contrast to the millisecond resolution of neural activity available in intracranial animal recordings. Moreover, numerous transmitter systems can be studied with similar spatiotemporal precision in animals, while human studies are currently limited to PET imaging, with very poor spatial and temporal resolution, and systemic pharmacological manipulations. Finally, it is important to acknowledge that the vast expansion of the frontal lobes in primates generally, and particularly in human subjects, may limit our ability to draw perfect parallels between humans and animal models.

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Figure 1. Cross-species representation of brain areas involved in habitual action selection
 Brain areas in blue demonstrate regions important for flexible behavior; orange represent areas controlling inflexible habits. In humans, note the diversity of frontal brain regions that contribute to the development of automatic responding. Brain areas in white circles are those that have been studied in rodents and primates, but their involvement in habit behavior in humans has yet to be investigated. Circles with gradient color indicate brain areas that show changes in activity when transitioning from flexible to inflexible behavior. Arrows indicate

nigral dopaminergic input to the dorsolateral striatum in rodents and putamen in humans and non-human primates.

Abbreviations: AMY, amygdala; BLA, basolateral amygdala; CeA, central amygdala; dACC, dorsal anterior cingulate; DLPFC, dorsolateral prefrontal cortex; DLS, dorsolateral striatum; DMS, dorsomedial striatum; GP, globus pallidus; ILc, infralimbic cortex; OFC, orbitofrontal cortex; PLc, prelimbic cortex; PMC, premotor cortex; SMA, supplementary motor area; SNc, substantia nigra pars compacta; vmPFC, ventromedial prefrontal cortex.

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