Published in final edited form as:

Physiol Behav. 2019 May 01; 203: 91–99. doi:10.1016/j.physbeh.2017.09.027.

Sex differences in incentive motivation and the relationship to the development and maintenance of alcohol use disorders

Jacqueline M Barker, PhD^{1,*} and Jane R Taylor, PhD²

¹Department of Neuroscience, Medical University of South Carolina, Charleston, SC 29425

²Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06519

Abstract

Despite considerable evidence of higher rates of alcohol use disorders (AUDs) in men than in women, there is a dearth of research into the underlying causes of this disparity. As the gap in high risk drinking between men and women closes, it is critical to disentangle the biological factors that may place men and women at different risk for the development of AUDs as well as AUD-associated health problems. While sex differences in alcohol drinking have been reported in animal models and in human alcoholics, it increasingly seems that consummatory behavior may be dissociated from propensity toward inflexible and cue-elicited drug seeking and taking that characterize alcohol use disorders. While much of this work was initially performed in males a growing, yet limited, body of literature suggests that there are sex differences in both cue reactivity, and further, the relationship between cue reactivity and the maintenance of addictive behavior, indicating that males may be at greater risk for the development of a subset of addiction-related behaviors independent of alcohol consumption. Here, we will review the current literature on sex effects on the relationship between incentive motivation and addictive behavior and discuss unanswered questions that we expect will inform the development of individualized and sex-specific treatment and prevention strategies for AUDs. We believe that a greater understanding of how sex interacts with in cue reactivity to independently mediate the drug taking and risk for the development of uncontrolled drug or alcohol-seeking and -taking will inform the development of individualized treatment and prevention strategies for addiction.

Keywords

sex differences; alcohol use disorders; female; incentive salience; sign- and goal-tracking; Pavlovian-to-instrumental transfer

*Corresponding author: Dr. Jacqueline M. Barker, Barker.jacqui@gmail.com, 67 President Street, Medical University of South Carolina, Charleston, SC 29425.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Significant sex differences have been identified in addictive behavior, but the relationship between sex and risk for the development of addiction is not entirely clear. Being male is consistently identified as a risk factor for alcohol use disorders (AUDs) (Kalaydjian et al., 2009). Historically, many studies have indicated that women drink less alcohol than men, and suffer fewer alcohol-related problems than men (Erol and Karpyak, 2015), but that those women that did consume ethanol excessively may be at elevated risk for the development of alcohol-associated health problems (Erol and Karpyak, 2015). More recent research indicates that the gap between male and female drinkers may be closing: while general increases in high risk drinking behavior and AUDs were observed from 2001–2002 to 2012–2013, the increase in both high risk drinking and the diagnosis of an AUD was considerably higher in women than in men (Grant et al., 2017; White et al., 2015), mirroring similar patterns in increases from the early 1990's (Keyes et al., 2008).

Existing research has suggested that men and women are differentially sensitive to risk-factors for AUDs. Notably, evidence from animal models suggest that sex differences in drinking behavior exist in the absence of social factors that may underlie differences in alcohol consumption, though this may be species and model specific. Multiple studies have seen higher levels of drinking at baseline in female rodents than in males, in both operant self-administration (Barker et al., 2010; Anderson and Spear, 2011; Bertholomey et al., 2016) and home cage drinking studies (Cailhol and Mormède, 2001; Tambour et al., 2008; Morales et al., 2015; Priddy et al., 2017), though this has not been universally observed (Varlinskaya et al., 2015). Interestingly, these sex-dependent differences in consumption may be mediated in part by organizing effects of gonadal hormones rather than circulating gonadal hormones (Almeida et al., 1998; Cailhol and Mormède, 2001; Barker et al., 2010; Priddy et al., 2017). Sex differences in alcohol consumption are less consistently observed in non-human primates, with some observing patterns similar to those reported in humans with higher consumption (Vivian et al., 2001) and greater maintenance of alcohol consumption among males (Grant and Johanson, 1998). Others, however, have observed greater alcohol consumption in female monkeys than in males (Juarez et al., 1993), suggesting that species and the precise drinking model utilized may contribute to sex differences in drinking behavior.

As rates of AUDs in women approach those of men, it becomes increasingly necessary to understand how biological differences may interact with drug exposure to produce differential risk for the development of AUDs and associated health problems. While drug *consumption* is clearly a critical component of addiction, much research has moved toward the investigation of models of cognitive control of drug seeking in order to gain insight into the differential drug-seeking behaviors that likely support addiction and vulnerability to develop addiction. Indeed, diagnosis of an AUD requires not simply extensive drinking, but also inflexible drinking that occurs despite adverse consequences, that is difficult to control/stop, and craving of drugs and alcohol. Relatedly, alcoholics show increased reliance on habit-like response strategies (Sjoerds et al., 2013). These inflexible behaviors can be modeled in animals, in tasks that investigate maintenance of reward seeking, such as habitual, compulsive, or extinction-resistant behaviors, as well as models of relapse

including reinstatement of drug-seeking behavior. Animal models of inflexible reward-seeking behaviors have provided considerable insight into neurobiology of addiction (Barker and Taylor, 2014; Gass et al., 2014; Serlin and Torregrossa, 2014; Barker et al., 2015) and indeed suggest that inflexible drug seeking may require different treatment strategies than flexible, goal-directed drinking (Hay et al., 2013).

What remains lacking, however, is knowledge about what factors predating exposure to alcoholism may produce risk for the transition to addiction or interact with alcohol exposure to facilitate and maintain addictive behavior. Because alcohol exposure itself is known to underlie many of the changes seen in addiction and dependence, understanding the neurobiology of risk requires identification of predisposed individuals prior to alcohol use. Aberrant cue-mediated behavior, such as increased craving/wanting in response to reward-paired stimuli (i.e., incentive salience), could mark risk for facilitated development of inflexible patterns of behavior including the formation of habitual and compulsive ethanol seeking and resistance to extinction that have been shown to be mediated by overlapping circuitry (Jentsch and Taylor, 1999; Flagel et al., 2008; Barker et al., 2012a; Saunders and Robinson, 2013). As the evidence grows showing that alterations in cue-mediated behavior in males may relate to the propensity to develop alcoholism-related behaviors, minimal research has investigated how these factors are related in females. Few papers exist assessing innate differences in cue reactivity between males and females, and further, whether cue reactivity measures predict the development addiction-related behaviors in females.

Here, we will discuss findings identifying relationships between cue reactivity and related neurobiological differences in the limbic cortico-striatal circuitry underlying incentive motivation that may predict risk for components of alcoholism. Further, we will describe the current understanding of sex differences in cue reactivity and incentive motivation. Finally, we will discuss known differences in the relationship between these innate differences in cue-mediated behavior and the development of inflexible, alcoholism-related behaviors that highlight the need to consider individual differences alongside sex and gender differences.

Cues in drug-seeking behavior

Over time and after repeated exposure, otherwise neutral cues that are associated with reward access or delivery are able to drive and invigorate behavior through the attribution of incentive motivational properties, often termed “incentive salience” (e.g., Robinson & Berridge, 2001). Across the acquisition of this relationship, a conditioned stimulus (CS; a tone) is paired with an unconditioned stimulus (US; reward). This Pavlovian conditioning occurs despite any action on the part of the animal – the CS is associated with the US independently of behavior. An animal’s understanding of the relationship between the CS and the US can be determined by measuring the ability of the CS to drive approach to the reinforcer, i.e., Pavlovian approach. Many models of addictive behavior posit that the attribution of incentive motivation to drug- and alcohol-paired cues can promote inflexible drug-seeking behavior (Jentsch and Taylor, 1999; Belin et al., 2009). While incentive motivational processes are a normal part of learning and memory, in drug users, these cues can initiate and maintain drug-seeking and taking.

Individual differences in incentive motivation predict propensity for addictive behavior

Cue reactivity in alcohol use disorders

In social alcohol drinkers, alcohol-paired cues can acquire incentive salience such that otherwise neutral cues can facilitate craving and orientation responses after pairing with alcohol (Field and Duka, 2002). Alcoholics show increased reliance on stimulus-response behavioral patterns (Sjoerds et al., 2013b), but whether these differences from the healthy controls reflect innate differences in automatic drug seeking or are acquired across drug use remains unclear. Chronic drug and alcohol use produces alterations in the brain's reward system that likely interacts with innate differences to produce alterations in incentive motivational processes that facilitate addictive behavior and reduce the cognitive control of actions needed to terminate drug seeking.

Alcohol cue exposure has been shown to produce a number of physiological and psychological responses in alcohol users (i.e., alcohol cue reactivity and cue-elicited craving, respectively), including changes in heart rate, salivation, markers of neuronal activity, self-reported craving and the willingness to 'work' for ethanol (Dager et al., 2013; Schacht et al., 2013; Van Dyke and Fillmore, 2015; Witteman et al., 2015). Notably, non-dependent "social" drinkers show facilitated operant alcohol seeking in response to alcohol-paired cues and subsequent drinking behavior, but this appears to occur at levels comparable to their typical patterns of drinking behavior (Van Dyke and Fillmore, 2015). In dependent individuals, however, exposure to alcohol-associated cues can promote excessive, uncontrolled drinking (e.g., Tiffany 1999). Interestingly, studies suggest that cue reactivity may be only loosely correlated with subjective craving. One possibility is that these cues elicit automatic drug-seeking behavior that thus mediates the relationship between cue reactivity and relapse, rather than a second order relationship mediated by cue-elicited craving. Indeed, an older study has suggested that reactivity to alcohol associated cues (as measured by salivation) was predictive of drinking behavior, while cue-elicited craving was not (Rohsenow et al., 1994), thus suggesting that it is not cue-elicited craving that is driving the inflexible drug seeking behavior that characterizes AUDs.

Aberrant cue reactivity has been identified in both alcoholics and individuals at risk for AUDs. Individuals with AUDs show increased reactivity to alcohol-associated cues (c.f., Schacht et al., 2013). In addition, increased cue reactivity has been shown to be associated with increased relapse after abstinence (e.g., Grusser et al., 2004, Beck et al., 2012). Importantly, factors that are predictive of increased risk for AUDs such as genetic polymorphisms that are associated with addiction (Kareken et al., 2010b), or a family history of AUDs (Kareken et al., 2010b; Oberlin et al., 2013) and decreased sensitivity to the sedating effects of ethanol (Bartholow, et al., 2010), are also predictive of enhanced reactivity to alcohol-paired cues. These data suggest that both individual differences as well as drug exposure can promote altered reactivity to alcohol associated cues.

Sex differences in cue reactivity and the relationship to alcohol use disorders in humans

Investigation into sex differences in incentive motivation is relatively lacking, though a growing body of literature has identified differences in alcohol cue reactivity between men and women. Indeed, alcohol-associated stimuli have been shown to only induce craving in male social drinkers (Willner et al., 1998). Notably, in social drinking males, craving was associated with alcohol cue-induced striatal activation, while this relationship was absent in women (Seo et al., 2011). Research in binge drinkers has identified sex differences in event cue reactivity to alcohol-associated stimuli. In particular, the authors observed that, consistent with the literature, binge drinkers showed elevated reactivity in one component of event-related potentials (Petit et al., 2013), which was greater in male binge drinkers than female binge drinkers suggesting that sex differences in cue reactivity are present in heavy drinkers. A single study has failed to identify differences in alcohol cue reactivity in dependent subjects (Rubonis et al., 1994). Though additional research is necessary, it is possible that males and females may differ in alcohol cue reactivity after minimal or moderate alcohol exposure, but do not differ after more extensive alcohol use.

Animal models of incentive salience and relationship to addictive behavior

As data from humans who show genetic risk for alcohol use disorders suggests that this inherited risk is associated with aberrant cue reactivity (Kareken et al., 2010b; Oberlin et al., 2013), it is interesting to speculate that risk for alcohol use disorders is in fact mediated by heritable differences in cue reactivity. However, in humans, determining a causal role for innate differences in cue reactivity and future drinking behavior is difficult. The use of animal models to assess the relationship between incentive salience and addictive behavior provides the significant advantage that it is possible to interrogate whether innate differences in response to reward-paired cues predate drug or alcohol exposure. In particular, we can determine whether drug and alcohol naïve animals show innate differences in behavioral models assessing incentive salience or cue-mediated behavior for non-drug rewards, allowing for assessment of any biological differences that may mediate these effects prior to any substance exposure.

Separate lines of research have investigated the relationship between cues and addiction related behavior. One model which has been extensively investigated is the “sign-tracker vs. goal-tracker” model (Flagel et al., 2009). This model focuses on individual differences in response to reward-predictive cues. Here, animals are trained that a cue predicts the delivery of a non-drug reinforcer. Over repeated pairings, these otherwise neutral cues that are associated with reward delivery are able to drive and invigorate behavior through the attribution of incentive motivational properties (e.g., Robinson & Berridge, 2001). A proportion of animals develop ‘sign-tracking’ phenotypes, and when the stimulus is presented, they engage with and interact with the stimulus, indicative attribution of incentive salience to the cue. Another subset of animals are ‘goal-trackers,’ that is, when a reward-predictive cue is presented, they orient to the location of the reward delivery. Interestingly, both sign- and goal-trackers have learned a stimulus-outcome association. What is distinct is the response to the stimulus presentation, which may be mediated by the attribution of value or incentive salience to the reward-predictive cue. Interestingly, locomotor response to novelty can predict subsequent sign- vs goal-tracker status: animals bred for a high response

to novelty were more likely to sign-tracking phenotypes, while animals with a lower response to novelty were goal-trackers (Flagel et al., 2010). In outbred populations, the proportion of animals showing sign-tracker vs goal-tracker phenotypes varies by study and even vendor (Fitzpatrick et al., 2013), suggesting that a number of factors may play a role in the attribution of incentive salience to reward-predictive cues. However, as sign- and goal-tracker phenotypes appear to be heritable in inbred rat lines, these rat lines may serve as a valuable model for the identification of genetic contributions to incentive salience as cue reactivity in humans is similarly heritable (Kareken et al., 2010a, 2010b; Dager et al., 2013; Oberlin et al., 2013).

In addition to response to novelty, sign tracking individuals differ from goal-trackers in a variety of drug-seeking and -taking behaviors (Flagel et al., 2008; Saunders and Robinson, 2013). In particular, sign-tracking phenotypes have been investigated in relationship to cocaine-related behaviors. Sign-tracking mice have been shown to have increased cocaine sensitization (Flagel et al., 2008), a model of cocaine-induced neurobehavioral plasticity. In addition, sign-trackers show an increased preference for cocaine over non-drug rewards (Tunstall and Kearns, 2015). Sign-trackers have also been shown to extinguish stimulus-outcome associations more rapidly than goal-trackers (Ahrens et al., 2015). Interestingly, this difference in Pavlovian extinction was not present for instrumental extinction, and sign- and goal-trackers extinguished action-outcome associations at the same rate.

Minimal research has assessed the relationship between incentive motivation phenotypes and ethanol self-administration specifically. What data do exist suggest that this relationship may be complicated. It has been reported that sign-tracking adult rats consume more ethanol than their goal-tracking counterparts, however, this relationship is dependent upon experience with reward-seeking during adolescence such that experiences that promote sign-tracking behavior similarly promote ethanol self-administration (Anderson and Spear, 2011). Recent research using alcohol-preferring (P) and non-preferring (NP) rats has identified higher rates of goal-tracking phenotypes in P rats than NP rats, while NP rats showed greater propensities toward sign-tracking phenotypes (Peña-Oliver et al., 2015). The authors suggest that this may be indicative of higher goal-oriented behavior in this rat line in general, thus driving both goal-tracking behavior and increased alcohol consumption, but it is unclear how this rat line compares to outbred animal models in this regard. Further, in a model of outbred rats, rats showing higher response to novelty (putative sign-trackers) showed a preference for water consumption over ethanol, while low responder rats (putative goal-trackers) showed no preference for water over ethanol, again suggesting that rats that are more likely to have goal-tracking phenotypes consume more ethanol (Gingras and Cools, 1995). As sign-tracking has consistently been associated with increased cocaine self-administration, these findings highlight the importance of not generalizing findings across drugs of abuse. In addition, while no goal-tracking phenotypes were associated with higher *consumption* of ethanol, it is unclear how sign- vs goal-tracker status predicts inflexible alcohol-seeking behavior in other models as these factors likely contribute independently to addictive behavior.

In addition to this model, Pavlovian approach and Pavlovian-to-instrumental transfer (PIT) models have been associated with alcohol-seeking behaviors. In particular, we have

observed that in an outbred mouse model, the ability of a reward-paired cue to elicit approach to a sucrose reinforcer (Pavlovian approach) was predictive of both habitual and compulsive-like reward seeking (Barker et al., 2014b). Specifically, high levels of Pavlovian approach for sucrose predicted alcohol seeking that was insensitive to changes in outcome value and action-outcome contingency that are indicative of inflexible, stimulus-response (S-R) habits, which are associated with addiction (Barker and Taylor, 2014; Everitt and Robbins, 2015). In addition, high Pavlovian approach predicted the development of compulsive-like ethanol seeking, or ethanol seeking that occurred despite adverse consequences.

Notably Pavlovian approach was not predictive of extinction or cue-induced reinstatement of ethanol seeking. In contrast, Pavlovian-to-instrumental transfer (PIT) was predictive of these behaviors. Pavlovian-to-instrumental transfer (PIT) paradigms enable the investigation of the ability of reward paired cues to invigorate instrumental responses, in which reinforcement is contingent upon an action, therefore allowing investigation of the interaction between Pavlovian stimulus-outcome (S-O) learning and instrumental response-outcome (R-O) learning. The ability of the stimulus to drive the response (S-R) is a measure of incentive motivation. Mice that showed high levels of PIT showed resistance to extinction of ethanol seeking as well as increased cue-induced reinstatement (Barker et al., 2012a).

Importantly, Pavlovian approach (PA) and Pavlovian-to-instrumental transfer (PIT) are both measurable in human and rodent populations, as well as other species including pigeon and monkey, enabling direct translation. Both PA and PIT have been shown to be altered in humans with AUDs (Garbusow et al., 2014; Wiers et al., 2014), though PA and PIT processes have not been directly related to specific components of AUDs. Interestingly, a number of theories have been proposed to explain PIT in addition the attribution of invigorating properties to the CS (e.g., Rescorla & Solomon, 1967; Holland & Gallagher, 2003). Alternative explanations include a two-process theory in which the outcome of an action can serve as a stimulus, thus continue to drive this stimulus-response behavior (e.g., Balleine and Ostlund, 2007).

Sex differences in cue reactivity and the relationship to ethanol seeking in animal models

Research into sex differences in the sign-tracking/goal-tracking paradigm have indicated that sex differences are dependent on a number of factors. In research done in mice, sex differences in sign-tracking and goal-tracking appear to be strain specific (Dickson et al., 2015). In all strains of mice tested, both male and female mice exhibited goal-tracking behavior. In contrast, the presence of sign-tracking behavior was sex- and strain-dependent. In most strains where sex differences were evident, male mice showed significant sign-tracking behavior, while female mice did not (one exception is the AJ strain where the pattern of sex differences was the opposite). In rats trained in this paradigm, it was observed that female Sprague Dawley rats acquired a sign-tracking phenotype more rapidly than male rats (Pitchers et al., 2015), but this sex difference was only apparent in this strain of rats and did not persist across training.

While sex differences in sign-tracking and goal-tracking behavior may be minimal or inconsistent, it remains critical to understand how differences in incentive motivation may

relate to addiction related behavior in adulthood. In animal models investigating locomotor response to novelty – which is predictive of sign- vs goal-tracking phenotypes (Flagel et al., 2010) - sex differences in cocaine seeking have been reported that do not interact with novelty-responding phenotypes (Cummings et al., 2011). In contrast, sex interacts with novelty seeking phenotypes to mediate overall cocaine self-administration (Davis et al., 2008) such that while greater response to novelty is predictive of increases in cocaine self-administration in both males and females, high responder females (putative sign-trackers) self-administer higher amounts of cocaine than high responder males.

In research investigating how sign- and goal-tracking behaviors may predict ethanol intake (Anderson et al., 2011), female rats were observed to show increased sign-tracking responses after training, but both males and females acquired sign-tracking behavior. Interestingly, no sex differences were seen in the relationship between behavioral phenotype and ethanol consumption. Indeed, while female rats consumed more ethanol overall, sign-tracking rats showed greater ethanol consumption than goal-tracking rats regardless of sex.

Sex differences in other putative measures of cue reactivity are similarly understudied. In a recent report, Quick and colleagues identified increased Pavlovian approach to the magazine in control female rats compared to male rats, as being predictive of increased propensity for the development of habitual ethanol seeking (Quick et al., 2014). However, in a mouse model that allows for dissociation of gonadal and genetic sex factors (termed the four core genotype model; FCG) (Arnold and Chen, 2009), we found that the relationship between PIT and ethanol seeking behaviors that was observed in outbred male mice was not present in female mice (see Fig. 1a, 1b). In these experiments, FCG mice were first trained in a PIT paradigm. Mice first learned that a cue (tone) was predictive of delivery of a non-contingent sucrose reward during Pavlovian training sessions. Mice were subsequently trained to make an instrumental response (lever press) for the sucrose reward. In a PIT probe test session, the ability of the sucrose-paired cue to invigorate instrumental responding was assessed in extinction (i.e., to sucrose was delivered). Animals were assigned to either Low or High PIT groups based on their performance during this test session. Following PIT assessment, mice were trained to make a different instrumental response (nose poke) for an unsweetened 10% ethanol reinforcer that was paired with a distinct cue (white noise). After stable responding was acquired, mice underwent extinction sessions until responding reached 10% of baseline presses. Finally, mice underwent a cue-induced reinstatement session in which responding was reinstated by presentation of the alcohol-paired cue. While we did not observe any sex differences in PIT status, we found that the relationship between PIT and ethanol reinstatement was unique to males. While high PIT male mice showed greater ethanol reinstatement than low PIT males, this relationship was absent in females. Together with findings from the sign-tracking/goal-tracking model, these data suggest that even in the absence of sex differences in cue reactivity, the relationship between cue reactivity and drug-seeking behaviors may be sex-specific. These findings are particularly interesting in light of findings from humans that men show greater cue reactivity (Petit et al., 2013) as well as cue-induced craving than women (Willner et al., 1998), suggesting that the relationship between cues and drug seeking may contribute more to the maintenance of alcohol seeking in non-dependent men.

Potential mechanisms underlying sex differences in incentive motivation

While the neuroanatomical substrates of incentive motivation for alcohol seeking are still being elucidated, a number of potential targets that may mediate sex differences have emerged. In both humans and animal models, differences in dopamine signaling have been shown to be related to cue reactivity and the attribution of incentive salience to cues. Indeed, significant data suggest that individual differences in prefrontal function may underlie differences in the transition from flexible drug use to addiction, and this may be in part mediate by differences in prefrontal dopamine function (George and Koob, 2010). Exposure to alcohol and alcohol-associated cues results in dopamine release in the nucleus accumbens (e.g., (Katner and Weiss, 1999; Doyon et al., 2003; Heinz et al., 2009). Recent research has shown that male and female binge drinkers are differentially sensitive to dopamine release after alcohol self-administration (Urban et al., 2010) with women showing lower dopamine release in the ventral striatum than men, though to our knowledge sex differences after alcohol cue exposure has not been assessed. As described above, striatal activation in males is associated with craving, though this effect is absent in women(Seo et al., 2011). It will be of interest to know whether sex differences in dopamine release to alcohol-associated cues can be identified. Preclinical models of sex differences in alcoholism are expected to be critical as alcohol craving and seeking may be modulated by gonadal hormones that can be carefully investigated or regulated in these paradigms for a more complete understanding of sex differences in these behaviors.

Though a complete understanding neurobiological differences that underlie sign-tracking and goal-tracking phenotypes does not yet exist, differences in accumbens dopamine signaling have been identified in this model (e.g., (Flagel et al., 2011). Indeed, data suggest that in both outbred rat populations and in rats that are bred based on their sign-tracking and goal-tracking status, dopamine release patterns in the nucleus accumbens are distinct (Flagel et al., 2011). In addition, high responder rats (putative sign-trackers) show reductions in D2 mRNA expression in the nucleus accumbens (Flagel et al., 2016), a potential mechanism by which incentive motivation is inherited. In contrast, alcohol preferring P rats who have increased propensity toward goal-tracking (Peña-Oliver et al., 2015), have lower D2 receptor binding in the accumbens, as well as other striatal subregions, compared to NP rats (McBride et al., 1993; Thanos et al., 2004). Notably, overexpression of D2 receptors in the accumbens of P rats reduces ethanol consumption (Thanos et al., 2004), suggesting potential divergence between the role of D2 receptors in the expression of sign vs goal-tracking phenotypes and ethanol consumption itself.

While differences in the dopamine system have not specifically been identified in innate differences in Pavlovian approach or PIT in outbred mice, dopamine signaling is heavily implicated in the both the acquisition of Pavlovian conditioning as well as the ability of Pavlovian conditioned cues to invigorate instrumental behavior for both food and alcohol (Lex and Hauber, 2008; Pielock et al., 2011; Wassum et al., 2011; Sciascia et al., 2014; Sparks et al., 2014; Schultz, 2015).

Significant sex differences in striatal dopamine signaling have been identified in both human and animals that have predominantly been linked to gonadal hormone modulation of

dopamine release (c.f., Becker and Taylor 2008; Yoest et al. 2014). Estrogens have been shown to enhance dopamine signaling and modulate learning and memory processes that are dopamine dependent (c.f., Jacobs and D'Esposito 2011). A substantial literature has focused on a role for ovarian hormone signaling in the regulation of dopamine release and drug self-administration (Becker, 1999; Anker and Carroll, 2010; Carroll and Anker, 2010; Hudson and Stamp, 2011). Additional work has indicated that testosterone attenuates striatal dopamine release (Hernandez et al., 1994; Shemisa et al., 2006), and studies from gonadectomized rats suggest that the effect of testosterone on dopamine release may be similar in the PFC (Aubele and Kritzer, 2011). Despite this clear role for sex hormones on dopamine signaling, minimal work has investigated how this would impact subsequent cue reactivity and mediate directly the relationship between cue reactivity and addiction-related behaviors.

In addition to the evidence that gonadal sex has an impact on sex differences in the neurobiology of addiction, the effects of sex chromosome complement have been appreciated more recently. With the advent of the four core genotypes mouse model discussed above (see Fig. 1a), research into the distinct contributions of gonadal and genetic sex have been possible. Indeed, sex chromosome complement has been shown to determine habit formation for both sucrose (Quinn et al., 2007) and ethanol (Barker et al., 2010). Sex chromosome complement has been shown to independently impact gene expression in reward related regions, including the striatum (Chen et al., 2009) where sex chromosome complement was shown to mediate the expression of prodynorphin, the endogenous ligand for the kappa opioid receptor, which has been implicated in regulation of dopamine signaling and in alcohol reward (Herz, 1997; Lindholm et al., 2007; Shippenberg et al., 2007). In addition, genetic sex effects have been identified in dopamine and serotonin receptor gene expression in the frontal cortex of mice after chronic stress (Seney et al., 2013). Genetic sex differences in BDNF-related genes were also observed, which are of note in light of a significant role for BDNF signaling in addiction (c.f., Barker et al., 2014a). These findings suggest that sex chromosome complement may interact with environmental factors such as chronic stress to alter gene expression, potentially indicating an additional mechanism through which sex differences in drug and alcohol dependence may emerge (Seney et al., 2013).

In addition to chronic stress effects, acute stress may have sex-specific effects on cue-mediated behavior. In humans, a large literature suggests that stress may enhance cue-induced craving and cue reactivity (c.f., (Seo and Sinha, 2014), and more recent work suggests that sex might mediate this relationship. For example, stimulation of the HPA axis via administration of yohimbine elevates cue-induced reinstatement in female, but not male, rats (Bertholomey et al., 2016). While we are not aware of data from alcoholics, administration of yohimbine to cocaine-dependent individuals results in elevations of cue-induced cravings selectively in women (Moran-Santa Maria et al., 2016). Together, these findings suggest that women may be particularly susceptible to stress facilitation of cue-induced reward seeking.

Incentive motivation phenotypes and individual differences in alcohol use disorders

Many researchers have recognized that individuals with AUDs vary widely in phenotype – including drinking patterns, age of onset, and sensitivity to alcohol's effects – and have used models to classify alcoholics based on these characteristics (c.f., Leggio, et al., 2009). Importantly, these differences are likely related to biological differences that may underlie these addictive phenotypes, including gene polymorphisms and treatment response (e.g., Enoch, 2003; Enoch, et al., 2003; Johnson, 2000). Typically, alcoholics are categorized by self-report along binary, either/or distinctions though there are models that propose multiple classifications. We propose a greater understanding of individual differences in cue reactivity may provide insight into the development and application of prevention and treatment strategies that are personalized based on sex, cue reactivity and additional risk factors (e.g., (Mann and Hermann, 2010). Indeed, these behavioral endophenotypes are marked by distinct neurobiological correlates that may lend themselves toward the advancement of personalized pharmacotherapeutics.

It is becoming clear that a direct link between individual differences in incentive motivation and separable components of inflexible alcohol seeking that characterize AUDs exists. Our findings suggest that the risk for habitual and compulsive behaviors may be separate from risk for resistance to extinction and reinstatement, and indeed the substrates that mediate risk for these different forms of inflexible alcohol seeking may be distinct. For example, we observed that innate differences Pavlovian approach were associated with alterations of serotonin receptor 5HT3 expression predicted risk for the development of habitual compulsive ethanol seeking, as well as the ability of 5HT3 antagonism to reduce compulsive behavior (Barker et al., 2012b). However, 5HT3 expression was not associated with reinstatement of ethanol seeking, suggesting that compulsive-like vs cue-induced reinstatement of ethanol seeking may be differentially sensitive to reduction with 5HT3 antagonism. In addition, findings from alcohol preferring P rats and high novelty responding rats suggest that the relationship between striatal D2 receptor may be complex, and that the role of D2 signaling in the attribution of incentive salience to alcohol-paired cues may depend on additional factors (McBride et al., 1993; Peña-Oliver et al., 2015; Flagel et al., 2016).

In addition to innate differences, others have demonstrated that drug and alcohol exposure itself impacts this circuitry. Together these findings suggest that individuals with innate versus acquired alterations in drug-seeking behavior may require distinct treatment and prevention strategies, and that the methods for targeting reduction in ongoing drug seeking versus the maintenance of abstinence may be separable. Though we have identified relationships between incentive motivation and propensity for addiction, this model has not yet been extended to assess whether these innate endophenotypes impact other risk factors, including (but not limited to) the sensitivity to stress and the stimulating effects of ethanol consumption, which will be necessary to develop a complete understanding of addiction. Importantly, these results also highlight the need for treatment of alcoholism based on the

behavioral phenotype of the individual and a shift toward the use of treatments that are targeted to particular disorder profiles.

Conclusions

Sex differences in alcohol use have long been observed, such that rates of both diagnosis of an AUD as well as high risk drinking patterns are more prevalent among men. However, in recent years, this gap has been closing as rates of problematic drinking patterns rise among women. In animal models, sex differences in drinking behavior are species dependent, but often reveal higher drinking in females than in males. More recent work suggests that models looking at consumption alone do not fully capture the complex factors that underlie the development and maintenance of AUDs. This significant body of literature has identified a relationship between cue reactivity and the risk for the development and persistence of AUDs, however much of this research has been conducted in male subjects (Schacht et al., 2013). What research does exist using women and female subjects has identified both innate sex differences in cue reactivity between males and females, as well as differences in the relationship between cue reactivity and the development and expression of alcoholism and alcoholism-related behaviors. In particular, while this field is in its infancy, findings from humans and animal models suggest that the positive relationship between innate differences in cue reactivity that predict subsequent alcoholism-related behavior that is regularly observed in males may be absent or attenuated in females. In contrast, a growing literature suggests that the ability of stress to facilitate cue-mediated reward seeking may be increased in both women and female animals. Together, these findings highlight the importance of initiatives promoting the inclusion of women and female subjects into investigation of AUDs as findings males are distinct from females both in the performance of addictive behavior as well as the underlying mechanisms that mediate the performance of alcoholism-related behaviors.

Acknowledgments

AA023141 (JMB), AA020135 (JMB), AA024499 (JMB), AA017776 (JRT), AA012870 (JRT).

References

- Ahrens, AM; Singer, BF; Fitzpatrick, CJ; Morrow, JD; Robinson, TE. Rats that sign-track are resistant to Pavlovian but not instrumental extinction. *Behav Brain Res.* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26235331> [Accessed August 4, 2015]
- Almeida OF, Shoaib M, Deicke J, Fischer D, Darwish MH, Patchev VK. 1998; Gender differences in ethanol preference and ingestion in rats. The role of the gonadal steroid environment. *J Clin Invest.* 101:2677–2685. [PubMed: 9637701]
- Anderson RI, Spear LP. 2011; Autoshaping in adolescence enhances sign-tracking behavior in adulthood: impact on ethanol consumption. *Pharmacol Biochem Behav.* 98:250–260. [PubMed: 21238477]
- Anker, JJ; Carroll, ME. Females Are More Vulnerable to Drug Abuse than Males: Evidence from Preclinical Studies and the Role of Ovarian Hormones; *Current topics in behavioral neurosciences.* 2010. 73–96. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21769724> [Accessed August 31, 2017]
- Arnold AP, Chen X. 2009; What does the “four core genotypes” mouse model tell us about sex differences in the brain and other tissues? *Front Neuroendocrinol.* 30:1–9. [PubMed: 19028515]

- Aubele T, Kritzer MF. 2011; Gonadectomy and hormone replacement affects in vivo basal extracellular dopamine levels in the prefrontal cortex but not motor cortex of adult male rats. *Cereb Cortex*. 21:222–232. [PubMed: 20466748]
- Balleine BW, Ostlund SB. 2007; Still at the choice-point: action selection and initiation in instrumental conditioning. *Ann N Y Acad Sci*. 1104:147–171. [PubMed: 17360797]
- Barker, JM; Corbit, LH; Robinson, DL; Gremel, CM; Gonzales, RA; Chandler, LJ. Corticostriatal circuitry and habitual ethanol seeking. *Alcohol*. 2015. Available at: <http://www.sciencedirect.com/science/article/pii/S0741832915202571> [Accessed May 19, 2015]
- Barker JM, Taylor JR. 2014; Habitual alcohol seeking: modeling the transition from casual drinking to addiction. *Neurosci Biobehav Rev*. 47:281–294. [PubMed: 25193245]
- Barker, JM; Taylor, JR; De Vries, TJ; Peters, J. Brain-derived neurotrophic factor and addiction: Pathological versus therapeutic effects on drug seeking. *Brain Res*. 2014a. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25451116> [Accessed December 3, 2014]
- Barker JM, Torregrossa MM, Arnold AP, Taylor JR. 2010; Dissociation of genetic and hormonal influences on sex differences in alcoholism-related behaviors. *J Neurosci*. 30:9140–9144. [PubMed: 20610747]
- Barker JM, Torregrossa MM, Taylor JR. 2012a; Low prefrontal PSA-NCAM confers risk for alcoholism-related behavior. *Nat Neurosci*. 15:1356–1358. [PubMed: 22922785]
- Barker JM, Zhang H, Villafane JJ, Wang TL, Torregrossa MM, Taylor JR. 2014b; Epigenetic and pharmacological regulation of 5HT3 receptors controls compulsive ethanol seeking in mice. *Eur J Neurosci*. 6:999–1008.
- Barker, JM; Zhang, Y; Wang, F; Taylor, JR; Zhang, H. Ethanol-Induced Htr3a Promoter Methylation Changes in Mouse Blood and Brain. *Alcohol Clin Exp Res*. 2012b. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22834954> [Accessed October 11, 2012]
- Bartholow BD, Lust SA, Tragesser SL. 2010; Specificity of P3 Event-Related Potential Reactivity to Alcohol Cues in Individuals Low in Alcohol Sensitivity. *Psychol Addict Behav*. 24:220–228. [PubMed: 20565148]
- Becker JB. 1999; Gender differences in dopaminergic function in striatum and nucleus accumbens. *Pharmacol Biochem Behav*. 64:803–812. [PubMed: 10593204]
- Becker JB, Taylor JR. 2008; Sex differences in motivation. *Sex differences and the brain: From genes to behavior*.
- Belin D, Jonkman S, Dickinson A, Robbins TW, Everitt BJ. 2009; Parallel and interactive learning processes within the basal ganglia: relevance for the understanding of addiction. *Behav Brain Res*. 199:89–102. [PubMed: 18950658]
- Bertholomey ML, Nagarajan V, Torregrossa MM. 2016; Sex differences in reinstatement of alcohol seeking in response to cues and yohimbine in rats with and without a history of adolescent corticosterone exposure. *Psychopharmacology (Berl)*. 233:2277–2287. [PubMed: 27048157]
- Cailhol S, Mormède P. 2001; Sex and strain differences in ethanol drinking: effects of gonadectomy. *Alcohol Clin Exp Res*. 25:594–599. [PubMed: 11329501]
- Carroll ME, Anker JJ. 2010; Sex differences and ovarian hormones in animal models of drug dependence. *Horm Behav*. 58:44–56. [PubMed: 19818789]
- Chen X, Grisham W, Arnold AP. 2009; X chromosome number causes sex differences in gene expression in adult mouse striatum. *Eur J Neurosci*. 29:768–776. [PubMed: 19250439]
- Cummings JA, Gowl BA, Westenbroek C, Clinton SM, Akil H, Becker JB. 2011; Effects of a selectively bred novelty-seeking phenotype on the motivation to take cocaine in male and female rats. *Biol Sex Differ*. 2:3. [PubMed: 21396095]
- Dager AD, Anderson BM, Stevens MC, Pulido C, Rosen R, Jiantonio-Kelly RE, Sisante J-F, Raskin SA, Tennen H, Austad CS, Wood RM, Fallahi CR, Pearlson GD. 2013; Influence of alcohol use and family history of alcoholism on neural response to alcohol cues in college drinkers. *Alcohol Clin Exp Res*. 37(Suppl 1):E161–71. [PubMed: 23078363]
- Davis BA, Clinton SM, Akil H, Becker JB. 2008; The effects of novelty-seeking phenotypes and sex differences on acquisition of cocaine self-administration in selectively bred High-Responder and Low-Responder rats. *Pharmacol Biochem Behav*. 90:331–338. [PubMed: 18445506]

- Dickson PE, McNaughton KA, Hou L, Anderson LC, Long KH, Chesler EJ. 2015; Sex and strain influence attribution of incentive salience to reward cues in mice. *Behav Brain Res.* 292:305–315. [PubMed: 26102561]
- Doyon WM, York JL, Diaz LM, Samson HH, Czachowski CL, Gonzales RA. 2003; Dopamine activity in the nucleus accumbens during consummatory phases of oral ethanol self-administration. *Alcohol Clin Exp Res.* 27:1573–1582. [PubMed: 14574227]
- Enoch M-A. 2003; Pharmacogenomics of alcohol response and addiction. *Am J Pharmacogenomics.* 3:217–232. [PubMed: 12930156]
- Enoch M-A, Schuckit MA, Johnson BA, Goldman D. 2003; Genetics of alcoholism using intermediate phenotypes. *Alcohol Clin Exp Res.* 27:169–176. [PubMed: 12605066]
- Erol, A; Karpyak, VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend.* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26371405> [Accessed October 1, 2015]
- Everitt, BJ; Robbins, TW. Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. *Annu Rev Psychol.* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26253543> [Accessed September 14, 2015]
- Field M, Duka T. 2002; Cues paired with a low dose of alcohol acquire conditioned incentive properties in social drinkers. *Psychopharmacology (Berl).* 159:325–334. [PubMed: 11862366]
- Fitzpatrick CJ, Gopalakrishnan S, Cogan ES, Yager LM, Meyer PJ, Lovic V, Saunders BT, Parker CC, Gonzales NM, Aryee E, Flagel SB, Palmer AA, Robinson TE, Morrow JD. 2013; Variation in the form of Pavlovian conditioned approach behavior among outbred male Sprague-Dawley rats from different vendors and colonies: sign-tracking vs. goal-tracking. *PLoS One.* 8:e75042. [PubMed: 24098363]
- Flagel SB, Akil H, Robinson TE. 2009; Individual differences in the attribution of incentive salience to reward-related cues: Implications for addiction. *Neuropharmacology.* 56(Suppl 1):139–148. [PubMed: 18619474]
- Flagel SB, Chaudhury S, Waselus M, Kelly R, Sewani S, Clinton SM, Thompson RC, Watson SJ, Akil H. 2016; Genetic background and epigenetic modifications in the core of the nucleus accumbens predict addiction-like behavior in a rat model. *Proc Natl Acad Sci.* 113:E2861–E2870. [PubMed: 27114539]
- Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, Akers CA, Clinton SM, Phillips PEM, Akil H. 2011; A selective role for dopamine in stimulus-reward learning. *Nature.* 469:53–57. [PubMed: 21150898]
- Flagel SB, Robinson TE, Clark JJ, Clinton SM, Watson SJ, Seeman P, Phillips PEM, Akil H. 2010; An animal model of genetic vulnerability to behavioral disinhibition and responsiveness to reward-related cues: implications for addiction. *Neuropsychopharmacology.* 35:388–400. [PubMed: 19794408]
- Flagel SB, Watson SJ, Akil H, Robinson TE. 2008; Individual differences in the attribution of incentive salience to a reward-related cue: influence on cocaine sensitization. *Behav Brain Res.* 186:48–56. [PubMed: 17719099]
- Garbusow M, Schad DJ, Sommer C, Jünger E, Sebold M, Friedel E, Wendt J, Kathmann N, Schlagenhauf F, Zimmermann US, Heinz A, Huys QJM, Rapp MA. 2014; Pavlovian-to-instrumental transfer in alcohol dependence: a pilot study. *Neuropsychobiology.* 70:111–121. [PubMed: 25359491]
- Gass JT, Trantham-Davidson H, Kassab AS, Glen WB, Olive MF, Chandler LJ. 2014; Enhancement of Extinction Learning Attenuates Ethanol-Seeking Behavior and Alters Plasticity in the Prefrontal Cortex. *J Neurosci.* 34:7562–7574. [PubMed: 24872560]
- George O, Koob GF. 2010; Individual differences in prefrontal cortex function and the transition from drug use to drug dependence. *Neurosci Biobehav Rev.* 35:232–247. [PubMed: 20493211]
- Gingras MA, Cools AR. 1995; Differential ethanol intake in high and low responders to novelty. *Behav Pharmacol.* 6:718–723. [PubMed: 11224374]
- Hay RA, Jennings JH, Zitzman DL, Hodge CW, Robinson DL. 2013; Specific and Nonspecific Effects of Naltrexone on Goal-Directed and Habitual Models of Alcohol Seeking and Drinking. *Alcohol Clin Exp Res.* 37:1100–1110. [PubMed: 23398292]

- Heinz A, Beck A, Grüsser SM, Grace AA, Wrase J. 2009; Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addict Biol.* 14:108–118. [PubMed: 18855799]
- Hernandez L, Gonzalez L, Murzi E, Páez X, Gottberg E, Baptista T. 1994; Testosterone modulates mesolimbic dopaminergic activity in male rats. *Neurosci Lett.* 171:172–174. [PubMed: 8084484]
- Herz A. 1997; Endogenous opioid systems and alcohol addiction. *Psychopharmacology (Berl).* 129:99–111. [PubMed: 9040115]
- Hudson A, Stamp JA. 2011; Ovarian hormones and propensity to drug relapse: A review. *Neurosci Biobehav Rev.* 35:427–436. [PubMed: 20488201]
- Jacobs E, D'Esposito M. 2011; Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. *J Neurosci.* 31:5286–5293. [PubMed: 21471363]
- Jentsch JD, Taylor JR. 1999; Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl).* 146:373–390. [PubMed: 10550488]
- Johnson BA. 2000; Serotonergic agents and alcoholism treatment: rebirth of the subtype concept—an hypothesis. *Alcohol Clin Exp Res.* 24:1597–1601. [PubMed: 11045870]
- Juarez J, Guzman-Flores C, Ervin FR, Palmour RM. 1993; Voluntary alcohol consumption in vervet monkeys: individual, sex, and age differences. *Pharmacol Biochem Behav.* 46:985–988. [PubMed: 8309979]
- Kalaydjian A, Swendsen J, Chiu W-T, Dierker L, Degenhardt L, Glantz M, Merikangas KR, Sampson N, Kessler R. 2009; Sociodemographic predictors of transitions across stages of alcohol use, disorders, and remission in the National Comorbidity Survey Replication. *Compr Psychiatry.* 50:299–306. [PubMed: 19486727]
- Kareken DA, Bragulat V, Dziedzic M, Cox C, Talavage T, Davidson D, O'Connor SJ. 2010a; Family history of alcoholism mediates the frontal response to alcoholic drink odors and alcohol in at-risk drinkers. *Neuroimage.* 50:267–276. [PubMed: 20004725]
- Kareken DA, Liang T, Wetherill L, Dziedzic M, Bragulat V, Cox C, Talavage T, O'Connor SJ, Foroud T. 2010b; A polymorphism in GABRA2 is associated with the medial frontal response to alcohol cues in an fMRI study. *Alcohol Clin Exp Res.* 34:2169–2178. [PubMed: 20698837]
- Katner SN, Weiss F. 1999; Ethanol-associated olfactory stimuli reinstate ethanol-seeking behavior after extinction and modify extracellular dopamine levels in the nucleus accumbens. *Alcohol Clin Exp Res.* 23:1751–1760. [PubMed: 10591591]
- Leggio L, Kenna GA, Fenton M, Bonenfant E, Swift RM. 2009; Typologies of alcohol dependence. From Jellinek to genetics and beyond. *Neuropsychol Rev.* 19:115–129. [PubMed: 19184441]
- Lex A, Hauber W. 2008; Shell mediate Pavlovian-instrumental transfer Dopamine D1 and D2 receptors in the nucleus accumbens core and shell mediate Pavlovian-instrumental transfer. *Learn Mem.* : 483–491. [PubMed: 18626092]
- Lindholm S, Rosin Å, Dahlin I, Georgieva J, Franck J. 2007; Ethanol alters the effect of kappa receptor ligands on dopamine release in the nucleus accumbens. *Physiol Behav.* 92:167–171. [PubMed: 17610914]
- Mann K, Hermann D. 2010; Individualised treatment in alcohol-dependent patients. *Eur Arch Psychiatry Clin Neurosci.* 260(Suppl):S116–20. [PubMed: 20953618]
- McBride WJ, Chernet E, Dyr W, Lumeng L, Li TK. 1993; Densities of dopamine D2 receptors are reduced in CNS regions of alcohol-preferring P rats. *Alcohol.* 10:387–390. [PubMed: 8216885]
- Morales M, McGinnis MM, McCool BA. 2015; Chronic ethanol exposure increases voluntary home cage intake in adult male, but not female, Long–Evans rats. *Pharmacol Biochem Behav.* 139:67–76. [PubMed: 26515190]
- Moran-Santa Maria MM, Baker NL, McRae-Clark AL, Prisciandaro JJ, Brady KT. 2016; Effects of yohimbine and drug cues on impulsivity and attention in cocaine-dependent men and women and sex-matched controls. *Drug Alcohol Depend.* 162:56–63. [PubMed: 26961964]
- Oberlin BG, Dziedzic M, Tran SM, Soeurt CM, Albrecht DS, Yoder KK, Kareken DA. 2013; Beer Flavor Provokes Striatal Dopamine Release in Male Drinkers: Mediation by Family History of Alcoholism. *Neuropsychopharmacology.* 38:1617–1624. DOI: 10.1038/npp.2013.91 [PubMed: 23588036]

- Peña-Oliver Y, Giuliano C, Economidou D, Goodlett CR, Robbins TW, Dalley JW, Everitt BJ. 2015; Alcohol-Preferring Rats Show Goal Oriented Behaviour to Food Incentives but Are Neither Sign-Trackers Nor Impulsive. *PLoS One*. 10:e0131016. [PubMed: 26098361]
- Petit G, Kornreich C, Verbanck P, Campanella S. 2013; Gender differences in reactivity to alcohol cues in binge drinkers: a preliminary assessment of event-related potentials. *Psychiatry Res*. 209:494–503. [PubMed: 23684055]
- Pielock SM, Lex B, Hauber W. 2011; The role of dopamine in the dorsomedial striatum in general and outcome-selective Pavlovian-instrumental transfer. *Eur J Neurosci*. 33:717–725. [PubMed: 21219479]
- Pitchers KK, Flagel SB, O'Donnell EG, Woods LCS, Sarter M, Robinson TE. 2015; Individual variation in the propensity to attribute incentive salience to a food cue: influence of sex. *Behav Brain Res*. 278:462–469. [PubMed: 25446811]
- Priddy BM, Carmack SA, Thomas LC, Vendruscolo JCM, Koob GF, Vendruscolo LF. 2017; Sex, strain, and estrous cycle influences on alcohol drinking in rats. *Pharmacol Biochem Behav*. 152:61–67. [PubMed: 27498303]
- Quick SL, Olausson P, Addy NA, Taylor JR. 2014; Repeated nicotine exposure during adolescence alters reward-related learning in male and female rats. *Behav Brain Res*. 261:171–176. [PubMed: 24333376]
- Quinn JJ, Hitchcott PK, Umeda EA, Arnold AP, Taylor JR. 2007; Sex chromosome complement regulates habit formation. *Nat Neurosci*. 10:1398–1400. [PubMed: 17952068]
- Robinson TE, Berridge KC. 2001; Incentive-sensitization and addiction. *Addiction*. 96:103–114. [PubMed: 11177523]
- Rohsenow DJ, Monti PM, Rubonis AV, Sirota AD, Niaura RS, Colby SM, Wunschel SM, Abrams DB. 1994; Cue reactivity as a predictor of drinking among male alcoholics. *J Consult Clin Psychol*. 62:620–626. [PubMed: 8063989]
- Rubonis AV, Colby SM, Monti PM, Rohsenow DJ, Gulliver SB, Sirota AD. 1994; Alcohol cue reactivity and mood induction in male and female alcoholics. *J Stud Alcohol*. 55:487–494. [PubMed: 7934057]
- Saunders, BT; Robinson, TE. Individual variation in resisting temptation: Implications for addiction. *Neurosci Biobehav Rev*. 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23438893> [Accessed May 28, 2013]
- Schacht JP, Anton RF, Myrick H. 2013; Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addict Biol*. 18:121–133. [PubMed: 22574861]
- Schultz W. 2015; Neuronal Reward and Decision Signals: From Theories to Data. *Physiol Rev*. 95:853–951. [PubMed: 26109341]
- Sciascia JM, Mendoza J, Chaudhri N. 2014; Blocking dopamine d1-like receptors attenuates context-induced renewal of pavlovian-conditioned alcohol-seeking in rats. *Alcohol Clin Exp Res*. 38:418–427. [PubMed: 24164210]
- Seney ML, Ekong KI, Ding Y, Tseng GC, Sibille E. 2013; Sex chromosome complement regulates expression of mood-related genes. *Biol Sex Differ*. 4:20. [PubMed: 24199867]
- Seo D, Jia Z, Lacadie CM, Tsou KA, Bergquist K, Sinha R. 2011; Sex differences in neural responses to stress and alcohol context cues. *Hum Brain Mapp*. 32:1998–2013. [PubMed: 21162046]
- Seo, D; Sinha, R. The neurobiology of alcohol craving and relapse; *Handbook of clinical neurology*. 2014. 355–368. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25307585> [Accessed August 31, 2017]
- Serlin, H; Torregrossa, MM. Adolescent rats are resistant to forming ethanol seeking habits. *Dev Cogn Neurosci*. 2014. Available at: <http://www.sciencedirect.com/science/article/pii/S1878929314000851> [Accessed January 6, 2015]
- Shemisa K, Kunnathur V, Liu B, Salvaterra TJ, Dluzen DE. 2006; Testosterone modulation of striatal dopamine output in orchidectomized mice. *Synapse*. 60:347–353. [PubMed: 16838357]
- Shippenberg TS, Zapata A, Chefer VI. 2007; Dynorphin and the pathophysiology of drug addiction. *Pharmacol Ther*. 116:306–321. [PubMed: 17868902]

- Sjoerds Z, de Wit S, van den Brink W, Robbins TW, Beekman ATF, Penninx BWJH, Veltman DJ. 2013a; Behavioral and neuroimaging evidence for overreliance on habit learning in alcohol-dependent patients. *Transl Psychiatry*. 3:e337. [PubMed: 24346135]
- Sjoerds Z, de Wit S, van den Brink W, Robbins TW, Beekman ATF, Penninx BWJH, Veltman DJ. 2013b; Behavioral and neuroimaging evidence for overreliance on habit learning in alcohol-dependent patients. *Transl Psychiatry*. 3:e337.doi: 10.1038/tp.2013.107 [PubMed: 24346135]
- Sparks LM, Sciascia JM, Ayorech Z, Chaudhri N. 2014; Vendor differences in alcohol consumption and the contribution of dopamine receptors to Pavlovian-conditioned alcohol-seeking in Long-Evans rats. *Psychopharmacology (Berl)*. 231:753–764. [PubMed: 24096535]
- Tambour S, Brown LL, Crabbe JC. 2008; Gender and Age at Drinking Onset Affect Voluntary Alcohol Consumption but Neither the Alcohol Deprivation Effect nor the Response to Stress in Mice. *Alcohol*. 32:2100–2106.
- Thanos PK, Taintor NB, Rivera SN, Umegaki H, Ikari H, Roth G, Ingram DK, Hitzemann R, Fowler JS, Gatley SJ, Wang G-J, Volkow ND. 2004; DRD2 gene transfer into the nucleus accumbens core of the alcohol preferring and nonpreferring rats attenuates alcohol drinking. *Alcohol Clin Exp Res*. 28:720–728. [PubMed: 15166646]
- Tunstall BJ, Kearns DN. 2015; Sign-tracking predicts increased choice of cocaine over food in rats. *Behav Brain Res*. 281:222–228. [PubMed: 25541036]
- Urban NBL, Kegeles LS, Slifstein M, Xu X, Martinez D, Sakr E, Castillo F, Moadel T, O'Malley SS, Krystal JH, Abi-Dargham A. 2010; Sex differences in striatal dopamine release in young adults after oral alcohol challenge: a positron emission tomography imaging study with [¹¹C]raclopride. *Biol Psychiatry*. 68:689–696. [PubMed: 20678752]
- Van Dyke N, Fillmore MT. 2015; Operant responding for alcohol following alcohol cue exposure in social drinkers. *Addict Behav*. 47:11–16. [PubMed: 25841089]
- Varlinskaya EI, Truxell EM, Spear LP. 2015; Ethanol Intake Under Social Circumstances or Alone in Sprague-Dawley Rats: Impact of Age, Sex, Social Activity, and Social Anxiety-Like Behavior. *Alcohol Clin Exp Res*. 39:117–125. [PubMed: 25623411]
- Wassum KM, Ostlund SB, Balleine BW, Maidment NT. 2011; Differential dependence of Pavlovian incentive motivation and instrumental incentive learning processes on dopamine signaling. *Learn Mem*. 18:475–483. [PubMed: 21693635]
- Wiers CE, Stelzel C, Park SQ, Gawron CK, Ludwig VU, Gutwinski S, Heinz A, Lindenmeyer J, Wiers RW, Walter H, Bermpohl F. 2014; Neural correlates of alcohol-approach bias in alcohol addiction: the spirit is willing but the flesh is weak for spirits. *Neuropsychopharmacology*. 39:688–697. [PubMed: 24060832]
- Willner P, Field M, Pitts K, Reeve G. 1998; Mood, cue and gender influences on motivation, craving and liking for alcohol in recreational drinkers. *Behav Pharmacol*. 9:631–642. [PubMed: 9862088]
- Witteman J, Post H, Tarvainen M, de Bruijn A, Perna EDSF, Ramaekers JG, Wiers RW. 2015; Cue reactivity and its relation to craving and relapse in alcohol dependence: a combined laboratory and field study. *Psychopharmacology (Berl)*. 232:3685–3696. [PubMed: 26257163]
- Yuest KE, Cummings JA, Becker JB. 2014; Estradiol, dopamine and motivation. *Cent Nerv Syst Agents Med Chem*. 14:83–89. [PubMed: 25540977]

Highlights

- Rates of alcohol use disorders are higher in men than in women, though this gap is closing
- Cue-mediated drug and alcohol seeking may be related to difficulty in terminating drinking
- Sex differences in the relationship between cue reactivity and drug seeking suggest that males may be at greater risk for cue-mediated alcohol consumption
- A greater understanding of sex differences in the relationship between incentive motivation and drug seeking are critical for developing treatment strategies

Figure 1.

(a) The four core genotypes (FCG) mouse model. In order to study the influence of sex chromosome complement and gonadal sex independently, MF1 FCG mice, in which the testis-determining gene, *Sry*, is deleted from the Y chromosome, were used. In breeders, an *Sry* transgene is inserted onto an autosome, resulting in testis formation. Because the *Sry* transgene is on an autosome, it segregates independently of sex chromosome. The activational effects of gonadal hormones were not considered as all mice underwent gonadectomy (GDX) or sham GDX at 45 days of age. (b) Sex chromosome predicts the relationship between incentive motivation and cue-induced reinstatement. FCG mice were XXF (gonadal and chromosomal females), XXM (chromosomal female, gonadal males), XYF (chromosomal male, gonadal female) and XYM (chromosomal and gonadal males). All mice were gonadectomized. High PIT mice show greater cue-induced reinstatement than Low PIT mice only in XY (chromosomal male) mice. There is no relationship between PIT

status and reinstatement in XX mice. * $p < .05$, ** $p < .01$. Error bars $\pm$ SEM. A three-way ANOVA (gonad $\times$ chromosome $\times$ PIT status) revealed an interaction between chromosome (XX vs. XY) and PIT (Low PIT vs. High PIT) on normalized responding in reinstatement (active response rate during the reinstatement session normalized to response rate on the last day of extinction; $F_{2,33} = 5.518$, $p = .028$). Post-hoc analyses indicate that only in XY mice does High PIT predict elevated reinstatement ($p = .03$), while in XX mice no difference was seen between reinstatement in High and Low PIT mice ($p = .2$). These data indicate that the observed relationship between PIT status and cue-induced reinstatement is only true in chromosomal males and that this relationship is lacking in chromosomal females.

Table 1**Glossary****Glossary**

Incentive – A stimulus that elicits approach/avoidance. Conditioned incentives are acquired by

Pavlovian conditioning and can function as conditioned reinforcers

Incentive salience – Attribution of want/desire to reward-associated stimuli

Cue reactivity – Physiological response to reward-associated stimuli

Cue-elicited craving – Psychological response to reward-associated stimuli

Goal-directed action – Behavior mediated by its relationship to its outcome and the value of the outcome (action-outcome [A-O] behavior). Actions are made with the intention of obtaining the goal (i.e., reinforcer) and are sensitive to devaluation of the goal

Habit – Behavior that is independent of the relationship to its outcome/the value of the outcome, but rather is elicited by a stimulus (stimulus-response [S-R] behavior). The reinforcer strengthens the S-R association rather than serving as a goal and is insensitive to devaluation of the goal

Compulsive behavior – Behavior that occurs despite adverse consequences

Extinction – Reduction in behavior following the omission of a previously learned outcome

Cue-induced reinstatement – Return to an extinguished behavioral response following the presentation of a previously reward-paired stimulus

Instrumental conditioning – The process by which a response is contingently associated with either reinforcement or punishment, that either increase or decrease the behavior, respectively

Pavlovian conditioning – The process by which a previously neutral conditioned stimulus (CS) comes to elicit a conditioned response (CR) as a result of a predictive contingency or temporal contiguity with either a reward or aversive unconditioned stimulus (US)

Pavlovian-to-instrumental transfer – The process by which a Pavlovian conditioned stimulus impacts motivational influence over instrumental responding for a reinforcer

Table 2

Cue reactivity is associated with alcoholism-related phenotypes. In both human and preclinical models, the presence of or increased risk for alcohol use disorders or alcoholism-associated behaviors is typically associated with increased reactivity to reward-associated cues. Notable exceptions include findings from Pena-Oliver and colleagues in which alcohol preferring (P) rats show less sign-tracking behavior than non-preferring (NP) rats.

Species	Cue Reactivity Measure	Alcoholism-related phenotype	Sex difference observed?	Reference
Human	Increased cue-induced activation in posterior cingulate, and other brain regions	Heavy drinking or alcohol use disorder		Schacht et al., 2013
Human	Increased cue-induced activation in multiple brain regions, including amygdala and cingulate	Heavy drinking	Females included, effect of gender not investigated	Dager et al. 2013
Human	Decreased cue-induced activation in multiple brain regions including fusiform gyrus, cerebellum	Family history of alcoholism	Females included, effect of gender not investigated	Dager et al., 2013
Human	Increased cue-induced activation in multiple brain regions, including orbitofrontal cortex, medial frontal cortex	Escalation of drinking	Females included, effect of gender not investigated	Dager et al., 2014
Human	Increased cue-induced activation in frontal cortex and VTA	Genetic risk (GABRA2 polymorphism)	Females included, effect of gender not investigated	Kareken et al., 2010
Human	Flavor cue-induced dopamine release in ventral striatum	Family history of alcoholism	Only males studied	Oberlin et al., 2013
Human	BOLD response to alcohol-associated words in multiple brain regions	Alcohol dependence	Only females studied	Tapert et al., 2004
Rat (outbred)	Sign-tracking (ST)	↑ Alcohol consumption	Relationship between ST and consumption in both sexes	Anderson and Spear 2011
Mouse	Pavlovian approach	↑ habitual alcohol seeking ↑ compulsive alcohol seeking	Only males studied	Barker et al., 2014
Mouse	Pavlovian-to-instrumental transfer	↓ extinction of ethanol seeking ↑ cue-induced reinstatement	Only males studied	Barker et al., 2012
Rat (P vs. NP)	Sign-tracking	↓ ethanol preference (NP rats)	Only males studied	Pena-Oliver et al., 2015