Human Laboratory Paradigms in Alcohol Research

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Background: Human laboratory studies have a long and rich history in the field of alcoholism. Human laboratory studies have allowed for advances in alcohol research in a variety of ways, including elucidating neurobehavioral mechanisms of risk, identifying phenotypically distinct subtypes of alcohol users, investigating the candidate genes underlying experimental phenotypes for alcoholism, and testing mechanisms of action of alcoholism pharmacotherapies on clinically relevant translational phenotypes, such as persons exhibiting positive-like alcohol effects or alcohol craving. Importantly, the field of human laboratory studies in addiction has progressed rapidly over the past decade and has built upon earlier findings of alcohol's neuropharmacological effects to advancing translational research on alcoholism etiology and treatment.

Methods and Results: To that end, the new generation of human laboratory studies has focused on applying new methodologies, further refining alcoholism phenotypes, and translating these findings to studies of alcoholism genetics, medication development, and pharmacogenetics. The combination of experimental laboratory approaches with the recent developments in neuroscience and pharmacology has been particularly fruitful in furthering our understanding of the impact of individual differences in alcoholism risk and in treatment response.

Conclusions: This review of the literature focuses on human laboratory studies of subjective intoxication, alcohol craving, anxiety, and behavioral economics. Each section discusses opportunities for phenotype refinement under laboratory conditions, as well as its application to translational science of alcoholism. A summary and recommendations for future research are also provided.

Key Words: Human Laboratory, Alcohol Phenotypes, Alcohol and Stress, Alcohol Craving, Impulsivity.

HUMAN LABORATORY STUDIES are not new to the field of alcohol research, as these paradigms have been utilized since the end of prohibition. Methods vary in these paradigms including alcohol administration by either the researcher (O'Connor et al., 1998) or the subjects themselves (King et al., 1997), cue administration directly related to alcohol (Monti et al., 1987) or to increase stress levels and subsequent desire to drink (Sinha, 2009), or administration of self-report rating scales on craving, impulsivity and anxiety in the presence of alcohol ingestion or alcohol cues (Petry, 2001). Human laboratory studies of alcohol have been used to understand the mechanisms underlying alcohol use, including reinforcement (Drobes and Anton, 2000), craving (Monti et al., 1987), and stress induction (Sinha, 2009), as well as to evaluate potentially efficacious treatments (Drobes et al., 2003). While clinical trials can tell us whether a treatment is effective but not why, human laboratory studies allow for parsing alcohol and medication response into discrete and quantifiable data. Expansion of such studies to include other variables of interest such as impulsivity and stress has allowed the field to address important and unique questions about alcoholism etiology and treatment. In this review, human laboratory phenotypes for alcoholism are discussed in the context of methodological advances, phenotype refinement, and translation to treatment.

This review is based on recent findings from the alcohol laboratory presented at the 2009 Annual Meeting of the Research Society on Alcoholism. We begin with an examination of individual difference variables that are associated with alcohol subjective responses measured in the human laboratory (Dr. Plebani). Next, we discuss anxiety models seeking to examine the negative reinforcing effects of alcohol (Drs. Morean and Corbin). We then move into a discussion of studies of alcohol craving, including cue-, alcohol-, and stress-induced craving paradigms (Dr. Ray). Finally, we discuss impulsivity and behavioral economic models applied to the elucidation of mechanisms of alcoholism risk (Dr. MacKillop and Mr. Amlung). Dr. King provides a synthesis of these findings in the context of human laboratory research on alcoholism and offers recommendations for future

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studies. Together, the studies discussed herein underscore the empirical and clinical utility of laboratory models applied to alcoholism, highlight opportunities for the new generation of laboratory studies in the field, and provide a translational framework for integrating experimental psychopathology, neurobiology, and the clinical treatment of alcohol use disorders (AUDs).

LABORATORY STUDIES OF ALCOHOL EFFECTS: INDIVIDUAL DIFFERENCES AND TRANSLATION TO TREATMENT

Alcohol self-administration studies have been widely used to examine acute intoxication and alcohol reinforcement and to examine the role of individual differences in such responses. While historically alcohol administration studies in humans examined social drinkers or persons at risk by virtue of family history or personality characteristics, in recent years, these studies have been expanded to include other at-risk groups, such as heavy drinkers or non-treatment-seeking alcohol-dependent individuals. During alcohol challenge studies, alcohol can be administered via 1 of 2 routes—orally or intravenously. In addition, it can be either self-administered by the subject or experimenter-administered. Our focus here is on oral alcohol studies, which provide subjects with the cues normally associated with drinking outside the laboratory (holding the drink, odor and taste, etc.). Ecological validity is high as oral alcohol studies can be designed to mirror alcohol use in the real world (Drobes et al., 2003; O'Malley et al., 2002).

An important application of human laboratory models of alcohol administration has been its use in the search for risk genes for alcoholism, including tests of candidate genes (e.g., Schuckit et al., 2005) as well as pharmacogenetic studies (Ray and Hutchison, 2007). This is an important next step given that until recently, self-reported biologic family history was the main method by which to establish linkage between one's alcohol responses and assumed inherited predisposition to alcoholism. Prior studies have focused primarily on the role of family history in predicting subjective responses to alcohol in the laboratory and the subsequent risk for the development of alcoholism. This approach has also been used to examine mechanisms of medications for alcoholism. To that end, a study by King and colleagues (1997) showed that naltrexone (NTX) blunts the subjective stimulation experienced after alcohol consumption only in individuals with a positive family history of alcohol dependence, but not among those with a negative family history. Subsequent studies also demonstrated that NTX elevates stress response, measured by adrenocorticotropic hormone and cortisol release among those with positive family history relative (King et al., 2002). More recent studies extended these findings from family history to candidate gene studies by demonstrating differential alcohol-induced subjective experiences of reward based on genotype (cf., Ray and Hutchison, 2004).

While alcohol administration studies have produced robust phenotypes capturing multiple dimensions of alcohol intoxication as well as theoretical models to explain these constructs (e.g., Newlin and Thomson, 1990), there is significant variability in the samples used in this line of research. For example, young adults have the highest rates of heavy drinking and are overall the healthiest, which allow for safe administration of higher doses of alcohol, making them a convenient population for alcohol challenge studies (cf., King et al., 1997; Ray and Hutchison, 2004). However, the treatment-seeking population is older and often has associated health problems. As such, more methodologically challenging laboratory studies of clinical groups is critical to generalizing to clinical populations (Blazer and Wu, 2009). So while older adults (55+) have traditionally been overlooked in alcohol administration studies, they comprise a large part of the treatment-seeking population (Verges et al., 2011).

Another methodological and sampling issue is the fact that the majority of human laboratory studies to date have enrolled predominantly European American samples. As such, questions regarding the generalizability of study findings to more racially diverse populations have not been sufficiently addressed. Data from the National Epidemiologic Survey on Alcohol and Related Conditions reveal that the overall proportion of African Americans with AUDs is almost identical to the proportion of Caucasians with AUDs (3.57 vs. 3.83%) (Grant et al., 2004). However, the likelihood of being alcohol dependent at a given age appears to differ by race, with a larger proportion of African Americans being alcohol dependent in their later years as compared to individuals of other races. There are only a few published studies of subjective alcohol responses in African Americans to date. This first study found a link between subjective responses to alcohol and the risk of heavy drinking and alcohol-related problems, such that acute simulation from alcohol administration was associated with increased risk (Pedersen and McCarthy, 2009). A recent study extended this research to the identification of candidate genes underlying subjective responses to alcohol in African Americans and found that the ADH1B*3, an alcohol metabolizing gene, was associated with higher levels of alcohol sedation, which in turn represents a protective factor against the development of alcoholism (McCarthy et al., 2010). Further, a reanalysis of the COMBINE Study focusing only on African Americans did not find a significant NTX effect, as reported for the full sample (Ray and Oslin, 2009). Together, these studies highlight recent progress and opportunities to apply alcohol administration models, and medication development efforts, to a wide range of patient populations and in combination with genetic variables.

A recently completed alcohol self-administration study among African Americans examined the effects of NTX on subjective intoxication in this population (Plebani et al., 2011). Non-alcohol-dependent adults of African descent ($n = 40$) were recruited for participation. After consenting,

genotyping, and completing the baseline assessment, each participant completed 4 separate alcohol challenge sessions separated by at least 10 days. During each of the sessions, participants were administered alcohol or sham drinks, after pretreatment with either NTX (50 mg/d) or placebo in a double-blind and crossover fashion. The order of the 4 sessions was randomly assigned. During each session, physiological and subjective responses were measured.

It was hypothesized that there would be effects, as measured by self-report measures, and by breath alcohol levels, of alcohol relative to sham drink. We further hypothesized that pretreatment with NTX would lead to a blunting of the reinforcing effects of alcohol relative to pretreatment with placebo, consistent with previous reports in Caucasian samples (King et al., 1997; Ray and Hutchison, 2007). Results supported the main effect of alcohol on measures of stimulation and sedation. However, there was no significant effect of NTX in blunting the rewarding subjective effects of alcohol in this social drinking population. Additional studies on the subjective effects of alcohol in African Americans who meet alcohol dependence criteria are needed. The study had several important strengths, including a sample comprised of African Americans of broader age range than typical alcohol administration studies.

In sum, there are important methodological issues and recent developments in the field of alcohol challenge studies. This line of research has refined to our understanding of how sample characteristics, study design, or both can be used to examine mechanisms of alcohol response in the human laboratory. Each of these, either alone or in combination, can help to parse out differences in alcohol response, which may ultimately lead to the development of targeted treatments for alcohol-dependent individuals with a given set of behavioral and genetic markers.

LABORATORY MODELS OF ANXIETY AND DRINKING: REEVALUATING THE TENSION REDUCTION MODEL

The Tension Reduction Model (TRM) of alcohol use focuses on principles of negative reinforcement, positing that individuals *learn* to drink to avoid the aversive experience of stress-induced negative emotional states (for a review, see Conger, 1951; Greeley and Oei, 1999). As such, risk for heavy drinking, the experience of alcohol-related problems, and relapse is thought to increase with the number of stressful life events an individual experiences. In this section, we will: (i) briefly describe expectancy (beliefs about alcohol effects) and pharmacology as bases for the tension-reducing effects of alcohol and (ii) review 2 recent studies examining the impact of sedative alcohol effects on alcohol use.

Consistent with the TRM, research has identified tension reduction expectancies as important determinants of drinking behavior (for a review, see Jones et al., 2001). Rather than exerting a direct effect on drinking, strong beliefs that alcohol will reduce tension are thought to give rise to *motivation* to drink (e.g., Kuntsche et al., 2006), such that individuals who drink specifically to cope with negative affect, like anxiety, are at increased risk for heavy use and alcohol-related problems (e.g., Catanzaro and Laurent, 2004; Kassel et al., 2000; Neighbors et al., 2007; Rafnsson et al., 2006). Although the research literature relating tension reduction expectancies to drinking behavior is convincing, it tells us little about the origins or veracity of these beliefs. The classification of alcohol as a sedative drug is consistent with the notion that tension reduction expectancies develop through the experience of pharmacological alcohol effects. However, laboratory-based studies suggest that the pharmacological effects of alcohol comprise both stimulant and sedative properties (Earleywine and Martin, 1993). Further, alcohol expectancies begin to develop well before alcohol use commences (Dunn and Goldman, 1998). Thus, to establish a pharmacological basis for the TRM, 2 critical lines of evidence must be demonstrated: (i) consuming alcohol must result in greater tension reduction than consuming placebo and (ii) experiences of tension reduction after consuming alcohol must predict subsequent drinking more strongly than experiences of tension reduction after consuming placebo.

With respect to the first issue, a review of the relationship between anxiety and alcohol use conducted over 20 years ago (Wilson, 1988) provides timely insight into the question "does alcohol reduce anxiety?" Wilson (1988, p. 371) argued that a more accurate phrasing of the question is: "At what dose, under which conditions, in whom, and on what measures does alcohol reduce anxiety?" Based on these factors, alcohol can create, exacerbate, reduce, or have no effect on anxiety. A large body of research supports this statement, as do prominent theories of the acute effects of alcohol on mood, cognition, and behavior [e.g., alcohol myopia (Steele and Josephs, 1990); appraisal disruption (Sayette et al., 2001); and stress response dampening (Sher et al., 2007)].

Although there is substantial research on the tension reduction properties of alcohol, there is a paucity of research examining the extent to which tension reduction increases subsequent drinking behavior in the human laboratory. However, 2 recent studies addressed the nature of the reinforcing properties of alcohol and evaluated the utility of conceptualizing tension reduction as a motivational influence for alcohol use. The first study (Corbin et al., 2008) evaluated the extent to which experiencing sedative alcohol effects (presumably including tension reduction) during an alcohol priming session motivated future ad libitum drinking under conditions of anticipatory anxiety. One hundred and seventy-four moderate-to-heavy drinking college students (50.3% male) were randomly assigned to consume either a placebo or a priming dose of alcohol. A target breath alcohol concentration (BrAC) of 0.06 g% was used to increase confidence that priming was not because of expectancies alone (e.g., Fillmore and Rush, 2001). Participants consumed 3 drinks over 30 minutes to reach the target BrAC. Fifteen minutes after consuming their final drink, participants rated

the extent to which they experienced a range of alcohol effects and, as a marker of reinforcement value, indicated how enjoyable they found the experience of each effect. Participants were then informed that they would be preparing and delivering a brief speech, a manipulation that has been shown to increase ad libitum consumption of alcohol (Higgins and Marlatt, 1975) and that was expected to increase the salience and desirability of the experience of sedative effects as a result of eliciting anticipatory anxiety. Before giving their speeches, participants were given ad libitum access to alcohol for 20 minutes or until they reached a BrAC of 0.12 g%. Based on the TRM, individuals who experienced pleasurable sedative effects during the alcohol prime were expected to consume more alcohol during the ad-lib session to modulate the anticipatory anxiety associated with giving a speech. Unexpectedly, the exact opposite pattern of results emerged. Participants universally evaluated sedative effects more negatively than stimulant effects, and neither expecting nor experiencing sedative effects during the priming dose predicted ad-lib drinking. Thus, to the extent that increased ad-lib consumption is a marker of reward or reinforcement, the study results suggested that stimulant effects are more reinforcing than sedative effects even under conditions of anticipatory anxiety. While inconsistent with the TRM, these findings are consistent with research suggesting that experiencing increases in alertness or positive mood after consuming alcohol primes further consumption both within the laboratory context (Corbin et al., 2008; Duka et al., 1998; Kirk and de Wit, 2000) and prospectively predicts future heavy drinking over time (King et al., 2011).

One possible explanation for the lack of support for the TRM in the study of Corbin and colleagues (2008) is that sedative alcohol effects are only reinforcing for individuals with strong beliefs about tension reduction or for those with high-level trait anxiety, anxiety sensitivity (Novak et al., 2003; Stewart et al., 1996), or neuroticism (Kuntsche et al., 2006). To explore this possibility, a second placebo-controlled study (Corbin et al., unpublished manuscript) examined the reinforcement value of sedative effects of alcohol for individuals who scored low, moderate, or high in trait anxiety on the Beck Anxiety Inventory (Beck et al., 1988). Participants consumed 3 drinks over 30 minutes, reaching a target BrAC of 0.08 g% in the alcohol condition. Fifteen minutes after their final drink, participants rated the extent to which they experienced a range of alcohol effects. Unlike the previous study, there was no anxiety manipulation or ad-lib drinking session. Instead, participants' self-reported craving for more alcohol following beverage administration served as the index of reinforcement value of alcohol effects. Within the alcohol condition, highly anxious individuals (relative to those low in anxiety) were expected to experience greater sedation, which, relative to the experience of other alcohol effects, was expected be most strongly tied to increases in craving for alcohol. Once again, results from this study did not support the TRM. Individuals high in anxiety did not report stronger experiences of sedation than their less anxious counterparts, and sedative effects were not associated with wanting more alcohol.

Although these 2 studies failed to support the TRM, the results must be considered in light of a number of important limitations. For both studies, the alcohol administration sessions occurred in a simulated bar laboratory. The novel, social drinking environment may have been more conducive to the experience of positive, stimulant effects than sedative effects—likely through a combination of expectancies and subjective experiences of pharmacological effects. It is possible that the utility of the TRM may be limited to certain settings or contexts (e.g., drinking alone or at home). Although the second study included individuals high in trait anxiety, it was not a clinical sample and diagnostic measures of anxiety disorders were not included. Future research is needed to determine whether a pharmacological basis for the TRM applies only to those with anxiety disorders or clinically significant anxiety symptoms.

In addition to the aforementioned methodological issues, existing measures simply may not provide an adequate test of the TRM because most do not assess a comprehensive range of alcohol effects. For example, the Subjective High Assessment Scale (Schuckit and Gold, 1998) focuses on negative sedative effects (slow, drowsy), while the Biphasic Alcohol Effects Scale (Martin et al., 1993) focuses on positive stimulant effects (elated, excited) and negative sedative effects (down, sedated). Measures fail to assess positive low arousal effects like anxiolysis as well as negative high arousal effects like anxiety that are central to the TRM. However, when mood measures, not specific to alcohol's effects, are added to an alcohol administration battery, a dimension of negative reinforcement emerged in factor analysis (Ray et al., 2009). Development of a more comprehensive subjective response measure may permit more complete tests of the pharmacological basis for the TRM.

In sum, recent alcohol administration studies have challenged the veracity of the TRM even within situations in which the model seems most likely to apply and for groups of individuals for whom the model seems most relevant; sedative effects do not appear to be experienced as desirable or to motivate alcohol use even under conditions of anticipatory anxiety or for individuals high in trait anxiety. While there is mounting evidence against a pharmacological basis for the TRM, current measures may not adequately capture the effects that are most relevant to evaluating the veracity of the TRM (e.g., relaxation, anxiety). Development of a more comprehensive subjective response measure will permit more complete tests of the pharmacological basis for the TRM and may also have additional utility. For example, high arousal negative effects of alcohol like aggression may be important predictors of alcohol-related risk-taking and negative consequences. Thus, a comprehensive measure of alcohol effects may contribute to our understanding of both internalizing and externalizing pathways to heavy drinking and related problems.

LABORATORY MODELS OF ALCOHOL CRAVING

Craving for alcohol is defined as a strong desire to consume alcohol. The proposed revisions to DSM-V have recognized craving as a symptom of AUDs, defined as "a strong desire or urge to use a specific substance" (www.dsm5.org). A longitudinal study found that alcohol craving was associated with the highest relative risk of alcohol dependence (de Bruijn et al., 2005). In addition, recent studies have advanced our understanding of the genetic bases of craving using self-report data in family-based genetic studies (e.g., Foroud et al., 2007), experimental designs in the laboratory (e.g., Hutchison et al., 2005), and neuroimaging paradigms (e.g., Filbey et al., 2008). Pharmacological studies have also used craving paradigms to screen (Mason et al., 2009) and to test (Hutchison et al., 2005) promising medications for alcoholism. Given the role of craving in the phenomenology and treatment of alcohol dependence, several approaches have been used to assess alcohol craving in the human laboratory.

In this section, we will: (i) briefly review the 3 methods for assessing alcohol craving, namely cue-induced, alcohol-induced, and stress-induced craving and (ii) describe a recent study seeking to dissociate stress-induced from cue-induced alcohol craving.

There is increased recognition that alcohol craving may be elicited through multiple methods, including cue exposure, stress induction, and alcohol administration. This is consistent with preclinical models of relapse (Epstein and Preston, 2003). Next, we review human laboratory models of craving.

Cue-Induced Craving

The cue-reactivity assessment paradigm is largely predicated on Pavlovian conditioned responses. Specifically, when an individual experiences repeated pairing of alcohol cues (e.g., sight, smell, and taste of the beverage) with alcohol consumption, over time, the alcohol cues themselves become conditioned stimuli, which elicit alcohol craving. These learned processes have been well documented in both human (O'Brien et al., 1990) and animal (Rodd et al., 2004) models. In the human laboratory, the cue-exposure paradigm consists of systematically exposing individuals to alcohol cues and assessing their associated urge to drink. Cue-reactivity procedures have been found to elicit craving among most heavy drinkers and alcohol-dependent individuals (Monti et al., 1987) and to yield valid and reliable assessments of alcohol craving (Monti et al., 2000, 2004; Payne et al., 1992). However, studies have suggested that only 50 to 65% of alcohol-dependent individuals display cue reactivity defined as a ≥ 1 standard deviation greater alcohol than water-elicited craving (Cooney et al., 1997; Litt et al., 1990; Rubonis et al., 1994).

The neural bases of cue reactivity have been highlighted in prominent neurobiological models of addiction (Kalivas and Volkow, 2005; Koob and Le Moal, 2008). Conditioned stimuli (cues) have been shown to trigger the release of dopamine in the ventral tegmental area, to the point where reward itself may no longer elicit dopamine release (Schultz et al., 1997). The nucleus accumbens is thought to mediate responses to alcohol cues via glutamatergic projections from the prefrontal cortex (Kalivas and Volkow, 2005). The conceptualization of cue-induced craving as "wanting" is consistent with the neural dissociation of reward proposed by Berridge and Robinson (2003; Berridge et al., 2009). In short, cue-elicited alcohol craving represents a useful translational paradigm for alcoholism.

Alcohol-Induced Craving

There is considerable evidence that small "priming" doses of alcohol increase the desire for alcohol (de Wit, 1996) and its consumption (de Wit, 2000). From a biologic standpoint, alcohol-induced craving has been posited to be associated with dopaminergic brain activity, primarily in the mesolimbic area (de Wit, 1996). A priming dose of alcohol has been used to induce craving in the laboratory and in brain imaging paradigms (Filbey et al., 2008). Priming paradigms represent an ideal analog for controlled drinking, which may be a treatment goal particularly among first-time treatment seekers (Locastro et al., 2008) or those with alcohol abuse or mild alcohol dependence (Marlatt and Witkiewitz, 2002). Sample characteristics, however, are critically important to the expression of the alcohol-induced craving as priming doses of alcohol have been shown to produce greater craving among heavier drinkers, as compared to social drinkers (Kirk and de Wit, 2000; de Wit, 2000). To date, the priming effects of small doses of and the effects of alcohol cues have been inextricably combined in oral alcohol administration procedures in which alcohol's pharmacology and alcohol cues are presented in tandem. Additional studies are needed to more fully dissociate alcohol cues from the pharmacological effects of alcohol. To that end, intravenous alcohol administration studies are ideally suited to dissociate alcohol's pharmacology from alcohol cues and to parse different aspects of motivation to drink induced through interoceptive and exteroceptive cues. Additional research is also needed to examine the effects of priming doses of alcohol on the course of drinking episodes among treatment-seeking individuals. Such approaches would help elucidate the pathway through which social drinking episodes turn into heavy drinking episodes, hence jeopardizing recovery efforts.

Stress-Induced Craving

The association between stress and alcohol use has been well documented in both the preclinical (Koob and Kreek, 2007) and human literature (Uhart and Wand, 2009). Laboratory models of stress and addiction have focused primarily on 2 methodologies, the use of an acute social stressor (e.g., the Trier Social Stress Test [TSST]; Kirschbaum et al., 1993) or the use of guided imagined exposure to stressful events

(Sinha, 2009). Studies using the TSST have suggested that stress produces mild increases in alcohol consumption (de Wit et al., 2003), decreases in subjective stimulant effects of alcohol (Soderpalm and de Wit, 2002; de Wit et al., 2003), and increases in the sedative effects of alcohol, but does not increase self-reported desire for alcohol following alcohol administration (Soderpalm and de Wit, 2002). A study found that males showed greater skin conductance and higher alcohol consumption to alcohol cues presented after stress induction (i.e., TSST) than females (Nesic and Duka, 2006). Although the TSST reliably produces elevations in cortisol and subjective stress, it has been criticized for its lack of external validity as the effects may be confined to social anxiety.

The second paradigm consists of guided-imagery exposure and is based largely on Lang's emotional imagery methodology (Lang, 1979; Lang et al., 1980). Specifically, this approach consists of obtaining information about recent stressful, neutral, and alcohol-/drug-related events in participants' lives and using that information to develop individualized scripts that are used to elicit stress under laboratory conditions. This approach has proven to be valid, reliable, and useful in advancing research on stress and addiction (Sinha, 2008) and may be particularly useful in explaining relapse (Sinha, 2007). As with the cue-induced craving paradigms, the integration of stress pathways into laboratory models is promising from a neurobiological perspective as theories of addiction have highlighted disruption in stress pathways as a central feature of addictive disorders (Koob and Kreek, 2007).

While these 3 methods reviewed above reliably produce the subjective experience of the craving in the human laboratory, less is known about how these methods interact. Preclinical studies often dissociate stress-induced from alcohol-induced reinstatement (Epstein et al., 2006; Heilig and Koob, 2007). Likewise, human laboratory models have investigated the relationship between stress and cue-induced craving. In particular, studies examined whether exposure to a stressor potentiates the experience of cue-induced craving. A study by Litt and colleagues (2000) using experience sampling found that participants reporting the most frequent urges were characterized as having more severe alcohol dependence as well as concurrent negative, high arousal mood states (anger or anxiety), which was the most powerful predictor of momentary urge to drink. Early work by Cooney and colleagues (1997) combining a negative mood induction with alcohol cue exposure found that both led to an increase in self-reported craving, yet their effects were additive, not interactive (or multiplicative). Similar findings have been recently reported by Thomas and colleagues (2011), who combined the TSST (or no stress condition) to alcohol cue exposure in a sample of non-treatment-seeking alcohol-dependent patients. Results revealed that the psychological stressor did not make the presentation of alcohol cues more potent and that stress had no effect on self-reported craving. Further research by Fox and colleagues (2007) using guided exposure to situations involving stress and alcohol cues found that while both stress and alcohol cues increased alcohol craving, each produced a dissociable psychobiological state. This dissociation suggested that while both parameters produced physiological arousal, a blood pressure increase was seen in the stress condition, whereas an increase in salivary cortisol was observed in the alcohol cue condition. Together, these results suggest that while the effects of alcohol cues and stress exposure are likely additive, they are not interactive as they do not potentiate one another. Instead, there is some evidence of dissociation between stress and cues at the psychobiological level of analysis.

To further this line of research, a recent laboratory study (Ray, 2011) combined imaginal stress exposure with alcohol cue exposure to assess the singular and additive effects of stress and cues in producing alcohol craving in heavy drinkers ($n = 64$). Results suggested dissociation between stress-induced and cue-induced craving for alcohol. Overall, individuals reached higher levels of craving upon exposure to alcohol cues and participants for whom alcohol cues were preceded by stress induction reported their craving to be at an intermediate point between baseline and post-cue exposure. Conversely, following the neutral imagery condition, subjective craving did not change until cues were presented. Similar results were found for mood variables, such as tension, which is often associated with the subjective experience of craving.

These findings suggest that stress and alcohol cues may not have interactive or even additive effects and instead may be dissociable in humans. This is also consistent with earlier work, suggesting that the presence of negative mood alone, following a mood induction, was sufficient to elicit alcohol craving regardless of cue exposure (Litt et al., 1990) and that negative mood predicted urges to drink (Litt et al., 2000) and relapse (Cooney et al., 1997). Likewise, a recent laboratory study found that an acute psychosocial stressor increased drinking in non-treatment-seeking alcoholics (Thomas et al., 2011). This study also examined genetic determinants of stress and cue-induced craving and found that a polymorphism of the corticotropin-releasing hormone-binding protein gene was associated with greater stress reactivity, while the Asp40 allele of the mu opioid receptor (OPRM1) gene was associated with stronger cue-induced craving for alcohol (Ray, 2011). Together, these findings provide an experimental framework for combining assessments of stress and cue-induced alcohol craving, which in turn can be used to interrogate genetic and pharmacological factors underlying these phenotypes. This approach has important translational value as it more closely parallels the preclinical literature and may be especially useful for testing mechanisms of medication effects, which may be more selective for stress or cue-induced mechanisms of craving (Heilig and Koob, 2007).

Last, while a variety of procedures have been used to elicit alcohol craving, including the presentation of alcohol stimuli via pictures, imagery, and smell taste cues, different

methodological approaches may be better suited for different research questions, such as brain imaging studies, and may be uniquely informative in experimental and clinical settings. For instance, a treatment study of alcohol-dependent patients comparing 2 measures of craving, cue-elicited versus self-reported using the Obsessive Compulsive Drinking Scale (Anton et al., 1996), found that cue-elicited craving at baseline was uniquely and positively associated with total number of drinks per drinking occasion over the course of treatment, suggesting that cue-elicited craving measured in the human laboratory may capture loss of control over drinking during treatment (Ray et al., 2006). In sum, the assessment of cue-induced craving in the human laboratory has proven to be a valid and efficient tool for research on alcoholism etiology.

BEHAVIORAL ECONOMIC PARADIGMS IN THE ALCOHOL LABORATORY

The field of behavioral economics is a hybrid discipline that integrates insights from economics and psychology to understand human behavior. This approach has been extensively applied not only to both normative behavior (Kahneman and Tversky, 2000) but also to pathological overconsumption, such AUDs and other types of addictive behavior (Vuchinch and Heather, 2003). According to the approach, alcohol and other drugs are powerful positive and negative reinforcers that are akin to any other reinforcers, comprising both benefits and costs. In the natural environment, where many concurrent behavioral opportunities are available, an individual's motivation to drink putatively reflects the value of alcohol compared with the values of all other potential opportunities in that environment (i.e., its relative value). In turn, AUDs reflect an acquired overvaluation of alcohol despite its negative physical and psychosocial consequences, although this overvaluation may result from a diversity of variables, including both intraindividual factors (e.g., intense subjective cravings) and environmental factors (e.g., absence of alternative reinforcers). In this section, we will review the methods and insights gained from 2 primary behavioral economic laboratory approaches—alcohol demand curve analysis and delayed reward discounting.

Quantifying the Relative Value of Alcohol via Demand Curve Analysis

A widely used behavioral economic approach to assessing the relative value of alcohol and other psychoactive drugs is the assessment of substance demand and, more specifically, demand curve analysis (for a review, see Hursh et al., 2005). Demand is an essential concept in economics and can be defined as the desired or actual level of consumption of a commodity at a single price or across prices. In the latter case, assessing demand across prices permits demand curve analysis, or the quantitative characterization of the relationship between consumption and cost. At zero or very low prices, demand for a reinforcer is at its maximum and tends to be relatively insensitive to initial increases in price; this portion of the demand curve is defined as "inelastic." However, as price increases, demand typically reaches a point at which the decreases in consumption outpace the increases in price; this portion of the demand curve is referred to as "elastic." Finally, beyond a certain price, consumption is completely suppressed. Across the 2 curves, individual features of demand and expenditure provide quantitative indices of relative value. In human laboratory studies on alcohol, demand for alcohol can be assessed using either progressive-ratio operant schedules (Hodos, 1961), where price is defined by increasing the behavioral response requirement, or an alcohol purchase task (APT; Jacobs and Bickel, 1999; Murphy and MacKillop, 2006), in which participants estimate their alcohol consumption at escalating monetary prices.

There is a large body of evidence indicating the importance of the relative value of alcohol as a determinant of consumption and problems. Early studies using residential laboratory approaches demonstrated that alcohol consumption is substantially determined by its behavioral costs and the presence of alternative reinforcers (for a review, see Bigelow, 2001). More recently, studies using APTs have revealed that indices of alcohol demand are significantly associated with level of alcohol use, alcohol problems, and severity of AUD symptoms (MacKillop et al., 2009, 2010a; Murphy and MacKillop, 2006; Murphy et al., 2009). These studies are further complemented by more naturalistic investigations that have alcohol use has been demonstrated to inversely vary with the availability of alcohol-free rewards in the natural environment (Tucker et al., 1994, 1995; Vuchinich and Tucker, 1996).

A recent development in this area is a focus on state changes in the relative value of alcohol. A recent study used a state-oriented APT and found that, compared to neutral cues, the presence of alcohol cues increased both craving and the value of alcohol (MacKillop et al., 2010b). This converges with several previous studies reporting correlations between subjective craving and the relative value of alcohol (MacKillop et al., 2007; McKee et al., 2008, 2009; O'Malley et al., 2002), but extends those findings in demonstrating that alcohol cues dynamically alter the value of alcohol. From a clinical standpoint, this provides a behavioral economic mechanism for the commonly observed shifts in preferences following treatment: although a person may aver the value of sobriety under neutral conditions, alcohol cues may drive up the value of drinking and, in turn, the probability of drinking itself. Further, a laboratory-based APT has been used to test the relative reinforcing value of alcohol and to serve as a drinking analog under laboratory conditions. For example, a study by O'Malley and colleagues (2002) gave participants the opportunity to drink up to 8 drinks or to receive US$3 for each drink not consumed over a 2-hour period. Results revealed that NTX-treated participants consumed fewer drinks than placebo-treated individuals. In short, a behavioral economic

approach to understanding alcohol consumption is both feasible and a useful tool to examining pharmacotherapy mechanisms of action, which may aid in screening and testing novel medications.

Delay Discounting: A Behavioral Economic Index of Impulsivity

A second widely used behavioral economic laboratory approach is delay discounting, an assay of impulsivity that measures how much a future reward is discounted based on its delay in time and putatively reflects an individual's capacity to delay gratification. In the laboratory, delay-discounting tasks typically involve participants choosing between smaller amounts of immediately available money and a constant larger delayed amount of money over several delay time intervals (e.g., $99 immediately vs. $100 in 1 week, $10 immediately vs. $100 in 2 weeks) (Bickel and Marsch, 2001; Reynolds, 2006). This permits the systematic identification of an individual's delay-discounting function, or the internal cognitive algorithm reflecting how rapidly the reward loses value because of its delay in time.

Numerous studies using healthy and clinical samples have characterized trait-level delay discounting as a behavioral process. In reference to alcohol misuse, a number of studies have revealed significantly more impulsive delay discounting in problematic or clinically diagnosed drinkers compared with healthy controls (Bjork et al., 2004; MacKillop et al., 2010a; Mitchell et al., 2005, 2007; Petry, 2001; Vuchinich and Simpson, 1998). Compared with controls, significantly greater discounting has also been consistently reported in individuals dependent on nicotine (e.g., Baker et al., 2003), opiates (e.g., Madden et al., 1997), and stimulants (e.g., Coffey et al., 2003) and exhibiting symptoms of pathological gambling (e.g., MacKillop et al., 2006). Moreover, there is increasing evidence that differences in discounting predate problems with addictive behavior. For example, in animal models, greater discounting is associated with drug use acquisition (Anker et al., 2009; Marusich and Bardo, 2009; Perry et al., 2005, 2007) and, in preschoolers, greater discounting is associated with adult drug use 20 years later (Ayduk et al., 2000). Importantly, discounting represents a potential translational phenotype in addiction. For example, a recent fMRI study has examined the neural substrates of impulsive choice in problem drinkers using a delay-discounting paradigm (Claus et al., 2011). This study found that individuals reporting greater alcohol problems showed stronger activation of the right cuneus, left anterior insula/orbitofrontal gyrus, right inferior frontal gyrus, inferior parietal lobe, left supplementary motor area, and middle temporal gyrus, during selection of larger delayed rewards. These findings suggest an increase in effort and neural resources needed to delay gratification among individuals with greater alcohol problem severity (Claus et al., 2011).

Interestingly, a number of laboratory studies have also revealed dynamic state changes in delay discounting. Acute withdrawal has been shown to augment impulsive discounting in primate models (Carroll et al., 2009) and in both opiate- and nicotine-dependent individuals (Badger et al., 2007; Field et al., 2006; Mitchell, 2004). Alterations in physiological states, such as sleep deprivation, also increase impulsive delay discounting (Reynolds and Schiffbauer, 2004). Studies on alcohol's effects on delay discounting have revealed somewhat ambiguous findings, with evidence that alcohol intoxication does not increase delay discounting (Richards et al., 1999) or actually makes discounting less impulsive (Ortner et al., 2003). Most recently, however, Reynolds and colleagues (2006) found evidence that alcohol intoxication does result in more impulsive delay discounting using a real-time discounting paradigm. In this study, healthy social drinkers completed the discounting task at 0.0 (placebo), 0.4, and 0.8 g/kg alcohol doses, and alcohol was found to increase impulsive responding measured by the experiential discounting task. While further studies are necessary to clarify these conflicting findings, emerging evidence supports the utility of this paradigm under a wide range of human laboratory conditions.

CONCLUSIONS AND FUTURE DIRECTIONS

Laboratory studies of acute responses to alcohol, alcohol cues, or other pharmacological and/or experimental manipulations have progressed in important ways and have the potential to greatly advance our understanding neurobehavioral mechanisms of alcohol effects on behavior. Such paradigms may (i) help identify important individual difference factors affecting alcohol response, such as personal traits, drinking characteristics, and genotype, (ii) aid in our understanding of the variability in cue and stress response and craving states, and (iii) inform and augment both clinical treatment trials and basic science and animal studies. In the next decade, advances from molecular, psychophysiological, and behavioral animal-based studies will need extensive translational cross-talk to human laboratory studies, as they represent an important bridge to establishing relevance of preclinical findings to humans. Similarly, phenomena discovered in the human laboratory will also need increased basic science translation in the future to examine precise genetic and epigenetic factors, neural mechanisms, and early developmental processes, many of which may be too invasive or unethical to study in human studies. A good example of such reverse translational approach has been recently published in which animal models have been used to elucidate the neural underpinnings of the genetic association between a polymorphism of the OPRM1 gene and subjective responses to alcohol in the human laboratory (Ramchandani et al., 2011). Finally, looking forward, the importance and relevance of translational studies between the human laboratory and intervention trials cannot be sufficiently underscored. In future studies, there needs to be better synergy between the goals of these studies, as well as their methods and participant selection, in order to more fully understand alcohol's

effects in particular subgroups, mechanisms of action of alcoholism pharmacotherapies, and the convergence of evidence from laboratory, proof-of-concept, to the placebo-controlled, double-blinded randomized trials. Moreover, human laboratory studies are an excellent fit for phase 2 medication development studies, given the feasibility and clinical relevance of the human laboratory models discussed above.

While over the past few decades, laboratory measures and paradigms have expanded with increased specification, sophistication, and validity, a number of unresolved issues and areas for further development remain. For example, while advances have been made in subjective assessment tools, further refinements are warranted. As discussed earlier in this paper, while alcohol may increase positive-like and stimulating effects in some drinkers, it also may increase positive sedating effects, such as feeling relaxed or calm, or negative stimulating effects (e.g., aggression). Development of psychometrically sound instruments to measure these, and other subjective effects sensitive to alcohol, will increase our scope and understanding of the differential effects of alcohol both across and within individuals. Finally, in the next decade, further research should more clearly establish which (and how) phenotypes derived from human laboratory paradigms are predictive of future drinking behavior, alcohol-related negative consequences, clinical diagnoses, and comorbidity. These methods will call for larger sample sizes and more diverse samples. There is also increasing need for consensus on what constitute gold standard laboratory methods and measures to assess predisposing factors such as subjective intoxication, alcohol craving, impulsivity, stress reactivity, and stress-response dampening. Common methods will increase consistency and allow for much needed replication of findings across studies.

On balance, human laboratory models of alcoholism have come a long way over the past 2 decades. In an increasingly interdisciplinary field, these models allow for much needed translation of preclinical findings to human samples. Likewise, these models allow for more mechanistic interrogation of clinical samples (e.g., mechanisms of medication response, mechanisms of relapse risk). Reverse translational approaches are also warranted. In sum, the successful application of human laboratory models in translational science hinges upon the effective dialog between clinical and preclinical scientists and upon the careful selection of methods and samples that can cut across disciplines.

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