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Experimental Psychopathology Paradigms for Alcohol Use Disorders: Applications for Translational Research

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Abstract

In spite of high prevalence and disease burden, scientific consensus on the etiology and treatment of Alcohol Use Disorder (AUD) has yet to be reached. The development and utilization of experimental psychopathology paradigms in the human laboratory represents a cornerstone of AUD research. In this review, we describe and critically evaluate the major experimental psychopathology paradigms developed for AUD, with an emphasis on their implications, strengths, weaknesses, and methodological considerations. Specifically we review alcohol administration, self-administration, cue-reactivity, and stress-reactivity paradigms. We also provide an introduction to the application of experimental psychopathology methods to translational research including genetics, neuroimaging, pharmacological and behavioral treatment development, and translational science. Through refining and manipulating key phenotypes of interest, these experimental paradigms have the potential to elucidate AUD etiological factors, improve the efficiency of treatment developments, and refine treatment targets thus advancing precision medicine.

Keywords

Experimental psychopathology; alcohol use disorder; alcohol administration; self-administration; cue-reactivity; stress

1. Experimental Psychopathology Paradigms for Alcohol Use Disorders

Alcohol use disorder (AUD) is characterized by a cluster of behavioral and physical symptoms involving prolonged and maladaptive alcohol use (American Psychiatric Association, 1994, 2013). Despite high prevalence rates and disease burden (Grant et al., 2015; Harwood, 2000), scientific consensus regarding the etiology of AUD has yet to be

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reached. Furthermore, while several treatment approaches have been developed for AUD, effect sizes are only modest (Anton et al., 2006; Ferri, Amato, & Davoli, 2006; Litten et al., 2012; Magill & Ray, 2009; Morgenstern & Longabaugh, 2000; Rubak, Sandbæk, Lauritzen, & Christensen, 2005).

Multiple experimental psychopathology paradigms in the human laboratory have been developed to address distinct aspects of AUD phenomenology. Controlled alcohol administration in the laboratory permits the fine-grained assessment of pharmacokinetic and pharmacodynamic responses to alcohol, which have long been proposed as important AUD risk factors (King, de Wit, McNamara, & Cao, 2011; Newlin & Thomson, 1990; Schuckit, 1984). Furthermore, self-administration paradigms permit objective behavioral assessments of alcohol consumption, motivation, and compulsive use which are central to addiction phenomenology (Koob & Volkow, 2009; Zimmermann, O'Connor, & Ramchandani, 2013). Bolstered in part by the assessment of cue-reactivity in the human laboratory, the importance of drug-paired cues has been advanced in several well-validated addiction theories (B. L. Carter & Tiffany, 1999; Robinson & Berridge, 1993). Lastly, the assessment of stress-reactivity in AUD aligns with important etiological models in both human and animal research which advance stress as both a risk and maintenance factor in addictive disorders (Cappell & Peter, 1972; Koob & Kreek, 2007; Levenson, Sher, Grossman, Newman, & Newlin, 1980).

In this article, we describe and critically review the major experimental psychopathology paradigms for AUD, with an emphasis on relative strengths, weaknesses, and methodological concerns. We then provide a discussion of the application of these paradigms to translational research including genetics, neuroimaging, treatment, and translational science.

1.1. Alcohol Administration Paradigms

Individuals vary dramatically in their subjective response to alcohol administration and these differences are related to alcoholism risk (King, de Wit, et al., 2011; King, McNamara, Hasin, & Cao, 2014; Ray, Mackillop, & Monti, 2010; Schuckit, 1984; Schuckit & Smith, 1996). Though many outcome variables can be measured in these alcohol administration studies with varying degrees of objectivity (e.g. static ataxia [body sway]), the subjective experience of alcohol intoxication, often termed subjective response to alcohol (SR) has emerged a primary predictive factor in human etiological models (e.g. Bujarski, Hutchison, Prause, & Ray, 2015; Bujarski & Ray, 2014; King, Roche, & Rueger, 2011; Morean & Corbin, 2010; Quinn & Fromme, 2011; Ray, Bujarski, & Roche, 2016; Ray, Mackillop, et al., 2010; Schuckit, Risch, & Gold, 1988; Schuckit & Smith, 1996).

Though no studies to date have observed increased drinking from participation in alcohol administration studies (Drobes & Anton, 2000; Pratt & Davidson, 2005; Sommer et al., 2015), alcohol administration studies, particularly those recruiting AUD patients, raise important ethical questions (Enoch et al., 2009). Consequently the National Advisory Council on Alcohol Abuse and Alcoholism has published research practice guidelines (2005). To that end, the inclusion of a brief concluding motivational interviewing session has

been shown to reduce participants' alcohol consumption (Bacio, Lunny, Webb, & Ray, 2014; W. R. Miller & Rollnick, 2002; Rubak et al., 2005).

1.1.1. Oral Alcohol Administration—The most common alcohol challenge paradigm involves the administration of controlled oral doses of alcohol. The earliest oral alcohol administration studies used predefined dosing based on body weight and sex (e.g. 0.75 ml of ethanol/kg body weight; Schuckit, 1984). While easily implemented, these paradigms produce wide variability in observed blood alcohol concentrations (BAC), introducing considerable noise in the alcohol response data. BAC is known to be affected by numerous individual difference and state factors including sex (Cole-Harding & Wilson, 1987), weight (Devgun & Dunbar, 1990), body water content (Goist Jr. & Sutker, 1985), and recent food consumption (Jones & Neri, 1991). Thus, researchers have developed mathematical models of alcohol pharmacokinetics resulting in more precise alcohol dosing algorithms (Brick, 2006; Friel, Logan, O'Malley, & Baer, 1999).

Ecological validity and relative ease of implementation represent the primary advantages of oral alcohol challenges. Target doses for these studies should be selected after weighing the reliability of alcohol responses against safety and time concerns. An intoxicating dose of 0.08 g/dl (or 80 mg%) is typical of oral alcohol challenge studies as this dose is commensurate with high-risk, or binge drinking (NIAAA, 2004). The wide variability in observed BACs, even when utilizing pharmacokinetic algorithms, represents a primary weakness. This methodological noise is then reflected in the outcome data, thus harming statistical power and reliability. Relatedly there is considerable variability in the time to peak BAC. Alcohol responses are biphasic in response profile, with stimulation more prevalent on the ascending limb and sedation on the descending limb (Newlin & Thomson, 1990). Thus inter-subject variability in time to peak BAC can result in limb-level variability that further contributes to methodological noise.

1.1.2. Intravenous Alcohol Administration—To precisely control BAC and to dissociate pharmacological effects from responses to alcohol cues, alcohol can be administered intravenously (Bujarski, Hutchison, Roche, & Ray, 2015; Li, Yin, Crabb, O'Connor, & Ramchandani, 2001; Ramchandani et al., 2002, 2006; Ray et al., 2013; Ray & Hutchison, 2004; Ray, Kahler, Young, Chelminski, & Zimmerman, 2008). In these paradigms, alcohol is prepared in a diluted saline solution (typical concentrations of 5–6% EtOH). Studies conducted in our research laboratory have implemented an infusion rate nomogram taking into account participant sex and weight (e.g. infusion rate of 0.166 ml/min × weight in kilograms for males, or 0.126 ml/min × weight for females). A major advantage of intravenous alcohol paradigms is the precise control over observed BAC. Participants are repeatedly breathalyzed, and upon reaching each target BAC, the infusion rate is halved to maintain relatively stable BAC during testing.

Recently, researchers have developed a physiologically-based pharmacokinetic (PBPK) model which precisely estimates BAC based on participant characteristics including height, weight, age, and sex while incorporating self-correcting model parameters based on observed BAC values (Plawecki, Han, Doerschuk, Ramchandani, & O'Connor, 2008). This model, implemented in the Computerized Alcohol Infusion System (CAIS; Zimmermann et

al., 2008; Zimmermann, O'Connor, & Ramchandani, 2013), permits fine-grained control of ascending limb BAC trajectories and, to a lesser extent, descending limb trajectories thus permitting systematic examination of limb effects and rate sensitivity (Wetherill et al., 2012). Furthermore, a recent extension of the PBPK model has shown that IV administration using CAIS is able to closely mimic subject-specific oral BrAC curves (Ramchandani, Plawecki, Li, & O'Connor, 2009).

Intravenous alcohol administration studies are thought to sacrifice ecological validity for greater experimental control and the elimination of visual, olfactory, and taste cues. Intravenous paradigms are significantly more expensive and require nursing support to place the IV catheter, a research pharmacy to prepare the EtOH-saline solution, and infusion supplies (IV pumps and lines). Implementing the CAIS system incurs additional costs as the infusion system requires a particular IV pump (iMed Gemini PC2-TX) and a dedicated computer to run the CAIS software.

1.1.3. Alcohol Clamp—The alcohol clamp paradigm involves maintaining steady state BAC over long periods of time through IV alcohol administration. Clamping permits the assessment of acute tolerance to alcohol's effects (Morzorati, Ramchandani, Flury, Li, & O'Connor, 2002; O'Connor, Morzorati, Christian, & Li, 1998; Ramchandani et al., 2006; Ramchandani, Bolane, Li, & O'Connor, 1999). Implemented in CAIS (Zimmermann et al., 2008), the alcohol clamp procedure has demonstrated remarkably stable BAC over time courses of hours.

The principle benefits of alcohol clamp paradigms lie in the unique parameters they are able to assess namely acute tolerance or sensitization and pharmacokinetic parameters including alcohol elimination rate (O'Connor et al., 1998; Ramchandani, Kwo, & Li, 2001). Long-term alcohol clamp procedures also allow for more robust assessments including behavioral tasks while at stable BAC. The limitations of intravenous alcohol administration are exaggerated in alcohol clamp paradigms insofar as the administration route and the BAC profile in clamp paradigms are quite different than those observed in the naturalistic setting.

1.2. Alcohol Self-Administration Paradigms

AUD involve the pathological consumption of alcohol and recurrent failure to limit use. Thus paradigms assessing self-administration benefit from strong face validity. Early studies recruited alcohol dependent subjects in an in-patient treatment context and permitted subjects to consume alcohol *ad libitum* over the course of days (Mello, 1972; Mello & Mendelson, 1965).

Self-administration paradigms examine operant conditioning factors such as reinforcement schedules, priming doses, alternative reinforcers, progressive reinforcement schedules, and punishment (e.g. monetary cost). Given the highly social nature of drinking, the presence of others was thought to influence self-administration in ways that were outside of experimental control, thus an early review recommended against testing participants in groups (Bigelow, Griffiths, & Liebson, 1975). Methodological advances in the observation and coding of social interactions however have renewed interest in social factors that

influence alcohol consumption (Fairbairn, Sayette, Levine, Cohn, & Creswell, 2013; Sayette et al., 2012).

1.2.1. Oral Alcohol Self-Administration—Modern self-administration paradigms can be grouped into two categories: the “de Wit Choice against Placebo Paradigm” and the “O’Malley Choice Against Money Paradigm” (Zimmermann, O’Connor, & Ramchandani, 2011). In the de Wit paradigm, participants initially sample various placebo or alcohol beverages over four separate sessions on different days and subsequently choose between the sampled beverages over three sessions (de Wit, Pierri, & Johanson, 1989; de Wit, Söderpalm, Nikolayev, & Young, 2003; de Wit, Svenson, & York, 1999; Duka, Stephens, Russell, & Tasker, 1998). The alcohol beverages consumed in this paradigm are laboratory prepared mixed drinks consisting of 10% ethanol in tonic water and/or fruit juice, and placebo beverages are identical but for a 1% ethanol concentration taste mask. Access to beverages in this paradigm is restricted to one drink per 10–15 minutes. The primary outcome is the number of alcoholic beverages chosen and the percent of participants who consumed any alcohol. BAC levels observed in this paradigm are typically quite low (~0.05 g/dl). The second and more widely used paradigm is the O’Malley paradigm (Anton, Drobes, Voronin, Durazo-Avizu, & Moak, 2004; Drobes, Anton, Thomas, & Voronin, 2003; McKee et al., 2009; McKee, O’Malley, Shi, Mase, & Krishnan-Sarin, 2008; O’Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002). After a priming dose, subjects are offered a tray of four prepared drinks standardized to body weight/sex and are instructed that they may consume as many drinks as they like over the next hour, or receive monetary compensation for the drinks not consumed (e.g. $3 per drinks). This procedure is repeated for a second hour with a second tray of drinks. Primary outcomes include the number of drinks consumed, observed BAC levels and the percent of subjects who abstained.

The disincentives in both paradigms are implemented to ensure that operant responding is for alcohol rather than general reward, or thirst. Settings vary dramatically including hospital rooms, clinical research labs, labs designed to look like a bar, and actual bars. Most self-administration studies include a priming drink with typical target BAC doses ranging from 0.02 – 0.06 g/dl, though larger priming doses were found to increase the percentage of participants who abstained (Zimmermann et al., 2011).

The benefits of oral alcohol self-administration paradigms include strong external and ecological validity, relative implementation ease and low cost. Weaknesses include the wide variability in BAC profiles and the small number of total drinks available to participants which in turn reduces outcome variance and can induce a response demand characteristic (Orne, 2009).

1.2.2. Computerized Alcohol Infusion System—The development of CAIS (originally termed Computer-Assisted Self-infusion of Ethanol [CASE]) permits intravenous alcohol self-administration. The most widely utilized CAIS self-administration paradigm is a free-access (i.e. FR1) paradigm at a dose of 0.0075 g/dl BAC per administration delivered over 2.5 minutes. A priming dose of four administrations ordered over 10 minutes followed by a 15-minute waiting period is typical. Outcome measures include the number of drinks ordered and maximum BAC. Though FR1 is most common, CAIS can flexibly implement

various reinforcement schedules including progressive schedules. Relatedly, Plawecki et al. (2013) have developed a response input system for CAIS that utilizes a sustained attention task to self-administer alcohol. Rather than simply pressing a button, participants are required to press and hold the response button and release within a small window of time to order an alcohol dose. By varying the duration of the release window this task is able to flexibly adapt to alcohol-related impairment in motor performance.

The CAIS self-administration paradigm has several distinct advantages. First, it produces highly controlled BrACs and controls for alcohol cues. Second, it delivers smaller doses of alcohol per administration, allowing participants to order many more "drinks" per session. Third, it implements a BAC safety limit temporarily inactivating the response button at pre-set BAC levels. Relatedly, intravenous administration is able to instantaneously halt the delivery of alcohol such that BAC immediately declines which is not possible with oral administration. Limitations of the CAIS paradigm include low ecological validity, as well as cost and complexity of implementation.

1.3. Cue-Reactivity Paradigms

The ability of drug-paired cues to elicit craving and approach behavior is a staple of multiple theories of addiction etiology (B. L. Carter & Tiffany, 1999; Robinson & Berridge, 1993, 2000, 2001; Tiffany, 1990). In the human lab, cue-reactivity is typically studied through the systematic presentation of drug-paired cues. Alcohol cue paradigms have been developed utilizing various modalities including *in vivo* and pictorial exposures, as well as imaginal, audio, video and virtual reality. For the purposes of this review, we will focus on *in vivo* and pictorial cue paradigms as they are the most widely implemented (Reynolds & Monti, 2013). Of note, initial evidence has suggested that laboratory cue-reactivity may prospectively predict treatment outcomes (Braus et al., 2001; Grüsser et al., 2004; Rohsenow et al., 1994). Lastly, similar ethical concerns to alcohol administration have been raised with respect to cue-reactivity paradigms (A. Carter & Hall, 2013) necessitating careful study design to minimize participant risk.

1.3.1. Pictorial Cue Paradigms—The most basic pictorial alcohol cue paradigm involves the presentation of alcohol related images (typically in blocks) followed by brief assessments of subjective state (e.g. craving). These paradigms are typically employed in neuroimaging studies of alcohol cue-reactivity (Courtney, Schacht, Hutchison, Roche, & Ray, 2015; Heinz et al., 2004; Mann et al., 2014; Schacht, Anton, Voronin, et al., 2013), where the primary outcomes are indicators of brain activation, especially in "reward regions" and top-down executive control regions (Courtney et al., 2015).

A widely-used behavioral task utilizing pictorial alcohol cues is the alcohol dot-probe task (Duka & Townshend, 2004; M. A. Miller & Fillmore, 2010; Townshend & Duka, 2001). The alcohol dot-probe measures attentional bias to alcohol-related images. The task involves presenting alcohol-related images and matched control images on a screen followed by a visual probe (e.g. an 'X') with the participant quickly identifying the location of the probe (i.e. left or right) by pressing a computer key. Reaction time (RT) to the visual probe is measured and the attentional bias outcome is indexed by the difference between alcohol and

neutral mean RTs. To reduce habituation, the task also contains filler trials with control images (Townshend & Duka, 2001).

Pictorial cues are extremely flexible in their combination with various research methods. The primary limitation is the relatively low salience of the cues. Generally, the alcohol-related images are selected in order to include all alcohol beverage types (e.g. beer, wine, liquor, and mixed drinks), and to include a range of preparations (e.g. bottled and prepared). As a result, the salience of the individual images may vary substantially within a subject based on their preferred beverage. Furthermore, the presentation of a generic alcohol-related picture without the potential for actual alcohol consumption may not elicit craving or physiological responses to the same extent as *in-vivo* cues.

1.3.2. *In Vivo* Alcohol Cue Paradigms—Pioneered by Monti (1987), the widely used *in vivo* cue paradigm begins with singly-tested participants completing baseline assessments followed by the presented of a neutral water cue. Participants listen to an audio recording instructing them to handle, smell, and manipulate the water beverage for 3 minutes. Following this, participants repeat the assessment battery and complete a brief relaxation exercise. Then participants are presented with their preferred alcoholic beverage including a prepared drink in the appropriate glassware and a branded bottle and listen to an analogous instructions set.

Order of presentation is a central methodological issue for this paradigm. While some have utilized counterbalanced orders (Sayette, Griffin, & Sayers, 2010), the presentation of drug-cues first produces strong carryover effects (Monti et al., 1987). Thus most studies utilizing *in vivo* alcohol cues forgo counterbalancing (Hutchison et al., 2001, 2005; Monti et al., 1999; Reynolds & Monti, 2013).

In vivo alcohol cue paradigms benefit from strong ecological validity as the participants are presented with their preferred alcoholic beverage, and are exposed to naturalistic drinking cues. The salience of the cue is high and utilizes multiple sensory inputs. Weaknesses include the variability in the drinking cue being presented which may produce noise in the data. The high potential for carryover effects also represents a significant limitation. Lastly, it has been noted that not all subjects are significantly reactive to alcohol cues, including some with alcohol dependence (Mason, Light, Williams, & Drobes, 2009; Rubonis et al., 1994)

1.4. Stress-Reactivity Paradigms

Several prominent etiological models suggest that stress serves as a risk factor for AUD (Cappell & Peter, 1972; Greeley & Oei, 1999; Koob, 2009; Koob & Kreek, 2007; Koob & Le Moal, 1997; Levenson et al., 1980). The causal role of stress in AUD is bolstered by the consistent finding that hypothalamic-pituitary-adrenal axis activity promotes alcohol seeking behavior in both the preclinical and clinical experiments (Thomas & Bacon, 2013). In the laboratory, two predominant paradigms assessing psychological stress (as opposed to physical or pharmacological stress which are less common to date) have been widely utilized: the Trier Social Stress Test (TSST: Thomas & Bacon, 2013) and the Guided Stress Imagery Task (Sinha, Fuse, Aubin, & O'Malley, 2000).

1.4.1. Trier Social Stress Test—Social stress tasks include public speaking tasks (Matthew Field & Quigley, 2009), social interaction tasks (Higgins & Marlatt, 1975), and mental arithmetic tasks (Pratt & Davidson, 2009). The TSST, which involves all three of these stressors is the most common (Kirschbaum, Pirke, & Hellhammer, 1993; Thomas & Bacon, 2013). First the participant is instructed to prepare for a mock job interview. Second, the participant is placed in a room in front of non-responsive confederates without their prepared notes. Third, the participant completes serial subtractions to the same unresponsive audience who notes each error. The TSST has been shown to produce robust increases in subjective and objective measures of stress response including dramatic increases in cortisol, heart rate, and blood pressure (Dickerson & Kemeny, 2004; Kirschbaum et al., 1993; Singh, Petrides, Gold, Chrousos, & Deuster, 1999). Despite these robust stress responses, increases in alcohol craving and self-administration have not been consistently observed (de Wit et al., 2003; Nesic & Duka, 2006; Söderpalm & de Wit, 2002; Thomas, Bacon, Randall, Brady, & See, 2011; Thomas, Randall, Brady, See, & Drobes, 2011); although variability in alcohol use among the samples may contribute to these inconsistent findings.

Strengths of the TSST include the salience and intensity of the stressor which results in robust increases in physiological stress response. Weaknesses include the reliance on social stress which may be of varying salience across individuals. The TSST is also relatively difficult to implement and time intensive in that it requires at least 15 minutes of participant time and multiple highly trained research assistants to serve as confederates.

1.4.2. Guided Imagery Task—In the addiction literature, the guided imagery task developed by Sinha and colleagues has become increasingly popular (Fox, Bergquist, Hong, & Sinha, 2007; Sinha, 2009, 2011; Sinha et al., 2008; Sinha, Catapano, & O'Malley, 1999; Sinha et al., 2000). In this paradigm, participants are asked to provide details about a current unresolved stressful situation to a trained research assistant. These details are then turned into an audio recorded script that the participant listens to during testing. Typically, this paradigm also includes a neutral script and alcohol-related scripts can be developed to serve as a cue condition. Generally both stress and alcohol imagery increase measures of craving, negative affect, and physiological reactivity (Sinha, 2011). The most rigorously controlled of these paradigms involve additional training in mental imagery to ensure the fidelity of the guided imagery task (Sinha, 2011).

Outcome variables in this paradigm include mood and craving measures, as well as psychophysiology and stress hormones. The guided imagery task has been shown to reliably induce negative emotionality and craving, though effects on objective measures are mixed (Thomas & Bacon, 2013). Initial reports of the predictive utility of stress imagery on treatment outcomes have been positive (Higley et al., 2011).

Strengths of the guided imagery task include the personalized nature of the stress, and the relative ease of implementation which allows this task to be combined with other novel assessments and laboratory paradigms. Weaknesses include the generally weak effects on physiological and hormonal stress outcomes and the inherent variability in stressor salience and type with personalized scripts.

1.5. Other Laboratory Approaches

These nine paradigms represent the predominant experimental approaches to cutting-edge human experimental AUD research. Other approaches such as pharmacologically-induced craving paradigms (Umhau et al., 2011), behavioral economic analysis (Bickel, Madden, & Petry, 1998; MacKillop & Murphy, 2007), and impulsivity measures (Courtney et al., 2012; Jentsch et al., 2014) have also contributed to the AUD literature tremendously, though we are unable to review them in this paper. Next we will provide a brief introduction to the application of these paradigms in translational research aiming to elucidate the etiology and treatment of AUD.

2. Experimental Psychopathology and Alcoholism Genetics

Twin studies reliably demonstrate that AUD is highly influenced by genetic factors (Verhulst, Neale, & Kendler, 2015). However, these broad disease-phenotype approaches are unable to elucidate the biobehavioral mechanism of risk conferred by specific gene variants. Consistent with an endophenotype approach in psychiatric genetics (Gottesman & Gould, 2003; Salvatore, Gottesman, & Dick, 2015), the utilization of experimental psychopathology paradigms in combination with genetic analysis uniquely allows researchers to map genetic factors onto specific, reliable, and clinically relevant laboratory phenotypes.

For example, alcohol administration studies using twins and sibling pairs have demonstrated that alcohol responses are highly heritable (Heath & Martin, 1991; Viken, Rose, Morzorati, Christian, & Li, 2003). Controlled alcohol administration has been used to identify pharmacokinetic variants in alcohol metabolizing genes encoding the alcohol dehydrogenase and aldehyde dehydrogenase enzymes (Luczak, Glatt, & Wall, 2006) which are associated with greater aversive responses to alcohol administration (Cook et al., 2005; Wall, Thomasson, Schuckit, & Ehlers, 1992). Genetic loci affecting pharmacodynamic alcohol responses span multiple neurotransmitter systems including GABA (Pierucci-Lagha et al., 2005; Ray & Hutchison, 2009; Roh et al., 2011), acetylcholine (Joslyn et al., 2008), serotonin (Schuckit et al., 1999), and endogenous opioids (e.g. OPRM1; Hendershot, Claus, & Ramchandani, 2014; Ray, Barr, et al., 2012; Ray et al., 2013; Ray & Hutchison, 2004). Early evidence of gene × gene interactions have also been observed suggesting that alcohol challenge paradigms may be sensitive to epistatic genetic effects (Ray, Bujarski, Squeglia, Ashenhurst, & Anton, 2014). Consistent with enhanced hedonic responses among G-allele carriers of the OPRM1 A118G locus (Ray & Hutchison, 2004), a recent study utilizing the CAIS demonstrated greater self-administration among G-allele carriers (Hendershot et al., 2014), though other studies utilizing oral alcohol self-administration were null (Anton, Voronin, Randall, Myrick, & Tiffany, 2012; Setiawan et al., 2011). These studies together have advanced subjective responses to alcohol as an endophenotype for AUD, thus providing much needed clarity regarding the mechanism of genetic risk (Ray, Mackillop, et al., 2010).

Though less numerous, similar empirical and theoretical research has been conducted with cue- and stress-reactivity paradigms. For example, cue-reactivity paradigms have shown sensitivity to genetic factors including OPRM1 (Ray, 2011; Van Den Wildenberg, Wiers, et al., 2007), corticotrophin-releasing hormone binding protein (Ray, 2011), and D4 dopamine receptors (DRD4) (McGeary et al., 2006), though some null findings exist (Van Den

Wildenberg, Janssen, Hutchison, Van Breukelen, & Wiers, 2007). Pictorial cue-reactivity paradigms implemented in the context of neuroimaging have also revealed genetic factors impacting alcohol cue-reactivity including Cannabinoid Receptor 1 (Hutchison et al., 2008), DRD4, and OPRM1 (Filbey et al., 2008; McClernon, Hutchison, Rose, & Kozink, 2007). Twin studies with the TSST have also demonstrated significant heritability (Kirschbaum, Wüst, Faig, & Hellhammer, 1992; Kudielka, Hellhammer, Kirschbaum, Harmon-Jones, & Winkielman, 2007). Driven by the well understood neurobiology of stress, candidate gene studies of stress-reactivity have focused on HPA-axis genetic variants including the Glucocorticoid Receptor and neuropeptide Y genes (Wüst et al., 2004).

Taken together, these studies suggest that the application of experimental psychopathology paradigms in genetics research may help elucidate biobehavioral mechanisms through which genetic variants confer risk for AUD. The utilization of multiple experimental psychopathology paradigms in future research would shed light on whether given genetic variants predict multiple behavioral phenotypes, or whether the variant is uniquely associated with a particular mechanism of risk. However, it is important to note that the behavioral genetics literature broadly has been plagued by publication bias which may result in inflated genetic effect sizes (Duncan & Keller, 2011; Hart, de Wit, & Palmer, 2013). Though speculative, by advancing candidate endophenotypes it is possible that experimental psychopathology paradigms may improve the reproducibility of behavioral genetics research.

3. Experimental Psychopathology and Neuroimaging

Addiction neuroscience research has benefit greatly from functional neuroimaging including both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Many high-quality imaging studies utilize paradigms developed and refined in the human behavioral laboratory and thus experimental psychopathology informs the development of functional neuroimaging tasks which in turn interrogate the biological bases of behavioral phenotypes. For example, in their systematic review and meta-analysis, Schacht et al. (2013) showed that presentation of alcohol cues robustly activated limbic and prefrontal regions of the brain including ventral striatum, anterior cingulate, and ventromedial prefrontal cortex. Their meta-analysis also identified several regions more active in AUD cases relative to controls including posterior cingulate, precuneus, and superior temporal gyrus. Furthermore, some early evidence suggests that functional neuroimaging cue-reactivity outcomes may predict relapse propensity (e.g. Bach et al., 2015; Beck et al., 2012; Grüsser et al., 2004; Schacht, Anton, Randall, et al., 2013; Schuckit et al., 2016; Seo et al., 2015).

While cue-reactivity paradigms represent the predominant approach in the neuroimaging literature, alcohol administration paradigms have also been utilized to examine the neurobiological correlates SR. For example, one study combined oral alcohol administration with PET suggesting that endogenous opioid activity in the nucleus accumbens and orbitofrontal cortex may contribute to the subjective rewarding effects of alcohol (Mitchell et al., 2012). Additionally, Ramchandani et al. (2011) demonstrated that intravenous alcohol administration via CAIS induced dopamine release in the striatum, and that the magnitude of

this dopaminergic response was modulated by OPRM1. FMRI studies have also observed alcohol effects on cerebral blood flow (Strang et al., 2014). In sum, by bridging the gap between well-validated behavioral phenotypes and measures of biological function, the application of experimental psychopathology paradigms to functional neuroimaging is poised to generate considerable insight into the clinical neuroscience of AUD.

4. Experimental Psychopathology and Alcoholism Treatment

Only three FDA approved pharmacotherapies currently exist for the primary treatment of AUD (Disulfiram, Acamprosate, and Naltrexone [oral and injectable]) and these medications have demonstrated only moderate efficacy (Jørgensen, Pedersen, & Tønnesen, 2011; Maisel, Blodgett, Wilbourne, Humphreys, & Finney, 2013). Similarly there are several empirically supported behavioral therapies for AUD including cognitive behavioral therapy, 12-step facilitation, and motivational interviewing, though the efficacy of existing behavioral treatments is only modest, particularly at more severe stages of alcoholism (Anton et al., 2006; Ferri et al., 2006; Magill & Ray, 2009; Rubak et al., 2005).

Relative to randomized clinical trials (RCTs), experimental psychopathology approaches represent an efficient strategy for AUD treatment development in terms of both expense and time (Litten et al., 2012; Ray, Hutchison, & Tartter, 2010). In addition to testing drug safety and tolerability, experimental psychopathology paradigms allow for the testing of clinically meaningful endpoints theoretically providing information about treatment efficacy and paving the way for RCTs. At present it is not known which paradigms are most effective for screening novel treatments, thus studies may employ multiple experimental paradigms to maximize the potential for detecting clinically-relevant effects. In addition to providing efficient screening of novel treatments, experimental psychopathology paradigms allow for the advancement of personalized treatment through elucidating the mechanism of action of efficacious treatments and identifying moderators of treatment response.

4.1. Experimental Psychopathology and Pharmacology

One proposed mechanism of action for AUD medication is the ability to “block the buzz” or potentiate the aversive aspects of alcohol intoxication might be effective treatment options (Heilig et al., 2010). Several medications with known clinical efficacy have been shown to blunt the rewarding effects of alcohol including naltrexone (King, Volpicelli, Frazer, & O’Brien, 1997; Ray & Hutchison, 2007), nalmefene (Drobes, Anton, Thomas, & Voronin, 2004), and topiramate (Miranda Jr et al., 2008). Medications have also been shown to increase aversive alcohol responses including varenicline (Childs, Roche, King, & de Wit, 2012; Fucito et al., 2011) and naltrexone (McCaul, Wand, Eissenberg, Rohde, & Cheskin, 2000; Ray, Hutchison, et al., 2008; Swift, Whelihan, Kuznetsov, Buongiorno, & Hsuing, 1994). Disulfiram represents an extreme example of this aversive mechanism; however, compliance concerns are substantial (Jørgensen et al., 2011). Though several medications have shown consistent effects in RCTs and alcohol challenge studies, other medications suggest these approaches are not perfectly correlated (Bisaga & Evans, 2006; Brasser, McCaul, & Houtsmuller, 2004; Leggio et al., 2013).

Targeting alcohol reinforcement and compulsivity, several AUD medications have also been shown to reduce oral self-administration, including naltrexone (Davidson, Palfai, Bird, & Swift, 1999; O'Malley et al., 2002; Setiawan et al., 2011) and varenicline (McKee et al., 2009). Furthermore, initial studies have suggested that naltrexone and acamprosate may owe some of their clinical efficacy to their ability to blunt reactivity to drug-paired cues (Miranda et al., 2014; Ooteman, Koeter, Verheul, Schippers, & van den Brink, 2007).

Through refining the phenotype of interest, experimental psychopathology has contributed to the development of personalized treatment. One salient example is the pharmacogenetics of naltrexone. Guided by the pharmacology of naltrexone, alcohol challenge studies have identified genetic moderators of naltrexone, most notably the A118G SNP of OPRM1 (Bond et al., 1998; Ray, Barr, et al., 2012; Ray, Bujarski, Chin, & Miotto, 2012; Ray & Hutchison, 2007). This pharmacogenetic effect has been translated to clinical trials, however with somewhat mixed results (Anton et al., 2008; Gelernter et al., 2007; Oslin et al., 2003, 2015). To explain these mixed results it has been argued on the basis of other experimental psychopathology research that OPRM1-naltrexone pharmacogenetics might be most salient in the earlier stages of AUD where reward drinking is more salient (Bujarski, Hutchison, Prause, et al., 2015; Bujarski & Ray, 2014; Koob & Le Moal, 1997; Ray, Barr, et al., 2012; Ray, Courtney, Bujarski, & Squeglia, 2012). Beyond naltrexone and OPRM1, the pharmacogenetics literature is expanding rapidly and continues to benefit from an experimental psychopathology approach (for review see Roche & Ray, 2015).

4.2. Experimental Psychopathology and Behavioral Treatment

While the pharmacological treatment literature has extensively utilized experimental psychopathology methods, the behavioral treatment literature is considerably less well developed. Merging experimental psychopathology paradigms and behavioral treatment, Wiers et al. (2009) have developed a paradigm to measure and retrain alcohol approach tendencies termed the alcohol approach/avoidance task (alcohol-AAT). Using this paradigm, Wiers et al (2011) conducted a randomized controlled trial in alcohol dependent patients of an adjunctive cognitive-bias modification intervention. In a brief intervention Wiers et al (2011) demonstrated improved treatment outcomes at one year follow-up thus demonstrating the potential to pivot experimental psychopathology paradigms to behavioral treatment. Furthermore, there is a growing interest in using experimental psyhcopathology methods coupled with neuroimaging to elucidate mechanisms of change in behavioral interventions for AUD (DeVito et al., 2012; Feldstein Ewing & Chung, 2013; Feldstein Ewing, Filbey, Hendershot, McEachern, & Hutchison, 2011).

5. Experimental Psychopathology and Translational Science

Ethical considerations restrict the level of experimental control and neurobiological precision of human research. Conversely, preclinical research benefits from strong neurobiological precision, yet the translational applicability of preclinical research is often merely assumed through face validity. Studies aiming to translate preclinical theories to human populations stand to bridge this gap with experimental psychopathology research representing a promising modality for these translational efforts.

Our laboratory has recently published a series of studies utilizing an intravenous alcohol challenge to test predictions derived from well supported preclinical models of alcoholism etiology. Specifically we explored the transition from positive to negative reinforcement, posited by the allostatic model of addiction (Koob & Kreek, 2007; Koob & Le Moal, 1997, 2005, 2008). In these data the coupling between alcohol-induced stimulation and alcohol craving (indexing positive reinforcement) was significantly greater in heavy drinkers, as compared to alcohol dependent participants (Bujarski & Ray, 2014). This diminished salience of the stimulant/hedonic effects of alcohol among alcohol dependent participants has since been replicated and extended in a larger sample including light-to-moderate drinkers (Bujarski, Hutchison, Prause, et al., 2015).

Experimental psychopathology paradigms have also tested translational predictions of the incentive sensitization theory (IST; Robinson & Berridge, 1993, 2000, 2001). IST suggests neurobiological dissociation between reward (‘liking’), and motivational salience (‘wanting’) and suggests that cues acquire pathological incentive motivation properties such that the cue “grabs attention, becomes attractive and ‘wanted,’ and thus guides behavior to the incentive” (Robinson & Berridge, 1993, p. 261). Alcohol challenge research in humans has experimentally demonstrated the dissociability of ‘liking’ and ‘wanting’ in light and heavy drinkers (Hobbs, Remington, & Glautier, 2005). Furthermore, an alcohol cue dot-probe task has demonstrated greater attentional bias to alcohol cues among heavy drinkers as compared to non-heavy drinkers (Duka & Townshend, 2004; Matt Field, Mogg, Zetteler, & Bradley, 2004; Townshend & Duka, 2001). In sum, the thoughtful application of experimental psychopathology methods represents a promising avenue for the much needed translation of preclinical neurobiological theories to human clinical populations.

6. Conclusion and Future Directions

In this systematic review we provided a review of the major experimental psychopathology paradigms developed to understand the etiology of AUD and develop more effective treatments. These methods include alcohol challenge, self-administration, cue-reactivity, and stress induction paradigms. In reviewing each paradigm, we provided a description of their implication and discussed their relative strengths and weaknesses. The trade-offs endemic to experimental research between internal and ecological validity appear throughout alcohol experimental psychopathology (e.g. between oral and intravenous administration). Thus future studies utilizing multiple paradigms with complementary strengths and weaknesses are warranted. Furthermore, efforts to standardize experimental procedures would advance the field by establishing testing guidelines and procedures, which in turn can promote greater consilience in the literature.

Relatedly, in the context of treatment development, studies should strive to utilize multiple paradigms assessing complementary mechanisms of action. By utilizing multiple paradigms, treatment development studies stand a better chance to determine therapeutic mechanisms of action and more effectively screen medications (Ray, Hutchison, et al., 2010). Though this strategy increases the likelihood of effective treatment screening, further research is needed to determine the degree to which these experimental psychopathology paradigms translate to treatment outcomes (Yardley & Ray, 2016).

In sum, the utilization of robust experimental psychopathology paradigms represents an integral and active area within AUD research. We contend that the effective utilization of these experimental paradigms and practices will permit the elucidation of AUD etiological factors, will improve the efficiency of treatment development, and will refine treatment targets permitting personalized medicine that will dramatically reduce the human and economic cost of AUD.

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Highlights

- Experimental psychopathology methods represent a cornerstone of alcoholism research
- We review major paradigms emphasizing implications, pros/cons and challenges
- We review the application of experimental psychopathology to translational research

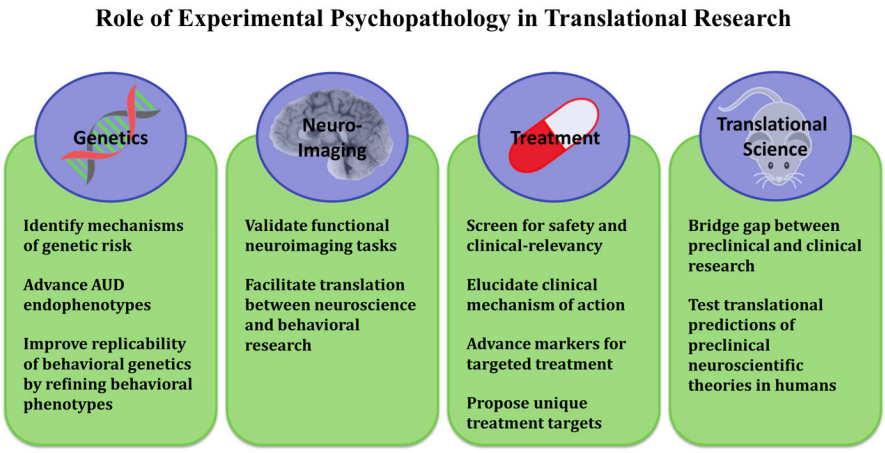

Figure 1.

The contribution of experimental psychopathology approaches to translational alcohol use disorder research.

Table 1

Overview of experimental psychopathology paradigms developed for alcohol use disorder research.

Class	Variant	Description	Dependent Variables	Strengths		Weaknesses		Key Citations
Alcohol Administration	Oral Administration	Participants are administered experimenter controlled doses of alcohol to target BrAC levels (doses often computed based on participant characteristics e.g. sex and weight)	Subjective Responses to Alcohol (e.g. BAES, SHAS, DEQ) Objective Responses (e.g. static ataxia, grooved pegboard)	**1** Ecologically valid route of administration **2** Relatively inexpensive		**1** Poor control over observed BrAC **2** Variability in time to reach peak BrAC		Schuckit, 1984 King et. al. 2011 Brick 2006
	Intravenous Administration	Ethanol-Saline solution infused into patents' veins to target BrAC's (infusion rate computed based on participant characteristics e.g. sex and weight)	Subjective Responses to Alcohol (e.g. BAES, SHAS, DEQ, POMS) Objective Responses (e.g. grooved pegboard)	**1** High level of control over BrAC trajectory. **2** Ability to maintain BrAC during testing		**1** Poor ecological validity **2** Relatively expensive		Ray & Hutchison 2004 Ray et al., 2009 Bujarski et al. 2015
	Alcohol Clamp	Alcohol administered intravenously in order to maintain stable BrAC over extended periods of time (e.g. > 1 hour)	Subjective Responses to Alcohol (e.g. BAES, SHAS, DEQ) Objective Responses (e.g. static ataxia, EtOH elimination rate)	**1** Permits rigorous examination of acute tolerance/ sensitivity **2** Highest level of control over BrAC		**1** Poor ecological validity **2** Relatively difficult to implement		Ramchandani et al. 1999 Ramchandani et al. 2006
Alcohol Self-Administration	Oral Self-Administration	Participant permitted to consume prepared mini-drinks often with a financial disincentive.	Indices of motivation for alcohol (e.g. number of drinks consumed, consumption rate, reinforcement breakpoint)	**1** Strong ecological validity **2** Relatively easily implemented		**1** Poor control over BrAC and timing **2** Low maximum number of		de Wit et al. 1989 O'Malley et al. 2002 McKee et al. 2009

Class	Variant	Description	Dependent Variables	Strengths		Weaknesses		Key Citations
		Typically a priming dose of alcohol is administered prior to self-administration.					drinks (~8 mini-drinks)	
	Computerized Alcohol Infusion System (CAIS)	Computer controlled alcohol infusion system that allows participants to self-administer IV mini-drinks. Typically a priming dose of alcohol is administered prior to self-administration.	Indices of motivation for alcohol (e.g. number of mini-drinks administered, peak BrAC, total alcohol infused, reinforcement breakpoint)	**1** **2** **3**	High level of control over the BrAC Flexible in BrAC curve parameters Implementable BAC safety limits	**1** **2** **3**	Poorer ecological validity Expensive Relatively difficult to implement	Zimmermann et al. 2008 Zimmermann et al. 2009 Hendershot et al. 2014
Alcohol Cue-Reactivity	*In Vivo* Alcohol Cues	Participants are presented with and asked to hold, smell, and manipulate their preferred alcoholic beverage. Cue reactivity is compared to a non-alcoholic beverage control.	Subjective craving (e.g. AUQ) Mood (e.g. POMS) Psychophysiology	**1** **2**	Strong ecological validity Highly salient cue presentation	**1** **2**	Variability in preferred drink and cue salience Carryover issues	Monti et al. 1987 McGeary et al. 2006
	Pictorial Alcohol Cues	Computerized presentation of alcohol-related cues versus control cues matched on multiple factors (e.g. beverages, color, and visual salience).	Subjective craving (single items) Reaction time to alcohol-paired target stimuli Psychophysiology	**1** **2**	Easily combined with other paradigms (e.g. neuroimaging) Ability to present many trials	**1** **2**	Relatively low salience cue Difficult to administer longer validated measures	Townshend & Duka 2001 Schact et al. 2013
Stress-Reactivity	Trier Social Stress Task	Participants perform socially stressful	Self-reported affect Subjective craving Cortisol	**1**	High intensity stressor	**1**	Relies on social stress	Söderpalm & de Wit 2002 de Wit et al. 2003

Class	Variant	Description	Dependent Variables	Strengths		Weaknesses		Key Citations
		activities in front of confederates (e.g. mental arithmetic and public speaking)	Psychophysiological measures (e.g. HR, BP)	**2**	Robust cortisol and psychophysiological responses	**2**	Requires confederates, increasing variability	
	Guided Imagery Task	Participants generate scripts of unresolved stressors, which are turned into an auditory stimulus presented to the participant.	Self-reported affect Subjective craving Cortisol Psychophysiological measures (e.g. HR, BP)	**1** **2**	Personalized stressor Relatively easy to implement	**1** **2**	Stressor tends to produce only mild cortisol responses Variability in the salience of the stressor	Sinha et al. 2000 Fox et al. 2007