Alcohol Cue Exposure Effects on Craving and Attentional Bias Among Underage Drinkers

By

Jason J. Ramirez

B.S., University of Vermont, 2005

M.S., Brown University, 2010

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Cognitive, Linguistic, and Psychological Sciences at Brown University

PROVIDENCE, RHODE ISLAND

MAY 2015

This dissertation by Jason J. Ramirez is accepted in its present form by the Department of Cognitive, Linguistic, and Psychological Sciences as satisfying the dissertation requirement for the degree of Doctor of Philosophy.

Date _____ _____

Ruth M. Colwill, Advisor

Date_____ _____

Peter M. Monti, Advisor

Recommended to the Graduate Council

Date_____ _____

William Heindel, Reader

Approved by the Graduate Council

Date_____ _____

Peter M. Weber, Dean of the Graduate School

CURRICULUM VITAE

Jason Ramirez

38 John St.
Providence, RI 02906
Jason_Ramirez@brown.edu

Box 1853
Brown University
Providence, RI 02912

EDUCATION

Ph.D. Department of Cognitive, Linguistic, and Psychological Sciences
Brown University
Expected Graduation Date: June 2014
Title: "Alcohol Cue Exposure Effects on Craving and Attentional Bias among Underage Drinkers"
Advisors: Dr. Ruth M. Colwill & Dr. Peter M. Monti

M.Sc. Department of Cognitive, Linguistic, and Psychological Sciences
Brown University
May 2010
Title: "Pavlovian Biconditional Discrimination Learning in the C57BL/6J Mouse"
Advisor: Dr. Ruth M. Colwill

B.Sc. Department of Psychology
University of Vermont
Cum Laude distinction
May 2005

PEER-REVIEWED PUBLICATIONS

Miranda, R., Monti, P. M., Ray, L., Trealor, H. R., Reynolds, E. K., RAMIREZ, J., Chun, T., Gwaltney, C. J., Justus, A., Tidey, J., Blanchard, A., & Magill, M. (2014). Characterizing subjective responses to alcohol among adolescent problem drinkers. *Journal of Abnormal Psychology, 123(1),* 117-129. doi: 10.1037/a0035328

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Miranda, R., Ray, L., Blanchard, A., Reynolds, E. K., Monti, P. M., Chun, T., Justus, A.,

Swift, R. M., Tidey, J., Gwaltney, C. J., & RAMIREZ, J. (2013). Effects of naltrexone on adolescent cue reactivity and sensitivity: an initial randomized trial. *Addiction Biology*. doi: 10.1111/adb.12050

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PUBLICATIONS SUBMITTED OR IN PREPARATION

RAMIREZ, J., Monti, P. M., & Colwill, R. M. (2014). *Alcohol cue exposure effects on craving and attention in college student drinkers.* Manuscript under review

RAMIREZ, J., & Miranda, R. (2014). *Effects of naltrexone on alcohol cue reactivity in the natural environment among heavy drinkers.* Manuscript in preparation

PRESENTATIONS

RAMIREZ, J., & Monti, P. M. (2013). Alcohol cue exposure effects on craving and attention in college student drinkers. Poster presented at Brown's Center for Alcohol and Addiction Studies 30th Anniversary Colloquium.

RAMIREZ, J., & Miranda, R. (2012). Contextual influences on adolescents' craving for alcohol in their natural environments: An ecological momentary assessment study. Poster presented at the 34th Annual Scientific Meeting of the Research Society on Alcoholism.

Morton, L. C., Mneimne, M., Kalafut, K., RAMIREZ, J., & Lytle, M. C. (2011). Graduate school in psychology: Information and experiences from EPAGS. Symposium presented at the 82nd Annual Meeting of the Eastern Psychological Association.

Miranda, R., Reynolds, E., Meehan, J., Justus, A., RAMIREZ, J., Tidey, J., Monti, P. M., Swift, R., MacKillop, J., & Chun, T. (2011). Biobehavioral mechanisms of naltrexone's action on drinking in adolescents: preliminary findings. Poster

presented at the annual meeting of the American College of Neuropsychopharmacology, Miami, Fl.

RAMIREZ, J. J. & Colwill, R. M. (2010). Pavlovian biconditional discrimination learning in the C57BL/6J mouse. Poster presented at the 81st Annual Meeting of the Eastern Psychological Association.

Fidler, T., Powers, M.S., RAMIREZ, J.J., Smitasin, P.J., Crane, A.T., Mulgrew, J.A., & Cunningham, C.L. (2009). Increasing the number of days of passive intragastric (IG) ethanol exposure increases IG ethanol self-administration in C57BL/6J and DBA/2J mice. Poster presented at the 32nd Annual Scientific Meeting of the Research Society on Alcoholism.

Fidler, T., Powers, M., RAMIREZ, J., & Cunningham, C. (2008). Optimizing passive Infusion parameters to produce ethanol self-infusion in C57BL/6J and DBA/2J mice. Poster presented at the 31st Annual Scientific Meeting of the Research Society on Alcoholism.

ABSTRACTS

RAMIREZ, J., & Miranda, R. (2012). Contextual influences on adolescents' craving for alcohol in their natural environments: An ecological momentary assessment study. *Alcoholism: Clinical and Experimental Research, Vol. 36(s1)*: 87A.

Miranda, R., MacKillop, J., Meehan, J., Justus, A., Tidey, J., RAMIREZ, J., Ray, L., Gwaltney, C., Swift, R., Rohsenow, D., McGeary, J., Carter, A., & Monti, P. (2011). Biobehavioral effects of topiramate among heavy drinkers. *Alcoholism: Clinical and Experimental Research, Vol. 35(s1):* 21A.

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Fidler, T., Powers, M., RAMIREZ, J., & Cunningham, C. (2008). Optimizing passive Infusion parameters to produce ethanol self-infusion in C57BL/6J and DBA/2J mice. *Alcoholism: Clinical and Experimental Research, Vol. 32*(*s1*): 215A.

GRANTS

1. Research Excellence Award, Jason Ramirez (PI) 4/2/13 - Current
   Center for Alcohol and Addiction Studies, Brown University
   "Alcohol Cue Exposure Effects on Craving and Attention in Late Adolescence"

These smaller grants, totaling ~$1500, provide support for the direct costs of research projects designed to provide pilot data to enhance the likelihood of future external grant support.

2. T32 (AA007459) Peter Monti (PI) 9/1/09 - 6/1/11
   NIAAA
   "Alcohol Intervention/Treatment Outcome Research Training"
   Role: Predoctoral Fellow
   This NIAAA-funded training grant prepares behavioral, social, health care, and medical scientists to conduct high-quality research in early intervention and treatment of alcohol abuse and dependence. The training program focuses on the development and implementation of on-site research under the supervision of trainee-selected faculty members.

PREDOCTORAL HONORS & AWARDS

RSA Student Merit Award, 2012 & 2014
Brown University Dissertation Research Fellowship, 2013
Brown University Teaching Fellowship, 2011-2012
Sheridan Teaching Center Certificate I, 2011
NIAAA Minority Travel Award for Center Director's Meeting, 2010

MEMBERSHIPS & POSITIONS

Graduate Student Liaison for Sheridan Teaching Center, 2011-2013
NIAAA T32 Training Conference Organizing and Planning Committee, co-chair poster session, September, 2011
Eastern Psychological Association, 2009-2012
Research Society on Alcoholism, 2008-current
Society for Neuroscience, Oregon Chapter 2007-2008

UNIVERSITY TEACHING ROLES

Teaching Assistant, January 2014 – May 2014
Department of Cognitive, Linguistic, and Psychological Studies, Brown University, Providence, RI
Course: Social Psychology (CLPS 0700), instructed by Fiery Cushman: Responsible for creating and grading coursework, holding office hours and presented midterm exam review

Teaching Assistant, September 2012 – December 2012
Department of Cognitive, Linguistic, and Psychological Studies, Brown University, Providence, RI
Course: Making Decisions (CLPS 0220), instructed by Steven Sloman: Responsible for creating and grading coursework, holding office hours and presented lecture titled "Substance Addiction and Decision Making."

Teaching Assistant, January 2012 – May 2012

Department of Cognitive, Linguistic, and Psychological Studies, Brown University, Providence, RI
Course: Quantitative Methods (CLPS 0900), instructed by Jack Wright, Ph.D.: Responsible for creating and grading coursework, holding interactive office hours in computer lab, and maintenance of course website.

Teaching Assistant, September 2011 – December 2011
Department of Cognitive, Linguistic, and Psychological Studies, Brown University, Providence, RI
Course: Introduction to Cognitive Science (CLPS 0020), instructed by Sheila Blumstein, Ph.D.: Responsible for creating and grading coursework, holding office hours and presented lectures titled "Studying Animal Models of Cognition," and "How to Write A Research Paper."

Teaching Assistant, January 2011 – May 2011
Department of Cognitive, Linguistic, and Psychological Studies, Brown University, Providence, RI
Course: Learning & Conditioning (CLPS 0100), instructed by Ruth Colwill, Ph.D.: Responsible for creating and grading coursework, holding office hours, delivering exam reviews, managing in-class iClicker software and presented lecture titled "Substance Addiction and Decision Making."

Guest Lecturer, February 2010
Department of Public Health, Brown University, Providence, RI
Course: Alcohol Use and Misuse (PHP 1540), instructed by Peter Monti, Ph.D.
Lecture Title: "Alcohol and the Developing Brain"

ACKNOWLEDGEMENTS

First I would like to thank my advisors, Ruth Colwill and Peter Monti. Ruth has truly shaped the way I think about science, and has always challenged me to be a better scientist. I owe much of my progress as a researcher and teacher to her mentorship. Peter has also shaped my scientific thinking, provided me with numerous opportunities for academic growth, and has helped me apply my background in learning and conditioning to the realm of public health. I couldn't have asked for a more exciting and fruitful collaboration and am grateful to each of them for fostering my unique fit at Brown. I would also like to thank the remaining member of my committee, Bill Heindel, who has also supported me since I arrived to Brown. I've greatly appreciated Bill's insights and he has been an invaluable source of knowledge in areas including but not limited to statistics and cognitive science. This guidance has helped me through each milestone of the program.

I want to also thank Robert Miranda Jr., who has met with me throughout my time at Brown and was crucial for the collection of data in Experiment 1. He has been like a third mentor to me and he has always had my best interests in mind while also providing me with valuable career advice. Further, I want to thank members of his lab including Justin Souliere, Jacqueline Lee, Shannon Hardy, and Bethany Rallis for their assistance with data collection on Experiment 1. I thank Jessica Faraj for her assistance with data collection on Experiments 2 and 3. I also thank my friends for their support including Katie Kalafut, Anna Hartley, David Freestone, and Steve Guglielmo among others from the CLPS Department.

Last, but certainly not least, my family has been an incredible source of support throughout my graduate career. First and foremost this includes my wife, Emily, who has had endless patience with me throughout the past six years, and has always supported my work. We've recently entered parenthood together and she has been the best mother of my daughter that I could ask for. It has been an incredible challenge as I finish my dissertation, but she has stepped up to this challenge in ways that I can never repay. There is not enough I can say to express my gratitude to her. I also want to thank my daughter Fiona for putting a smile on my face no matter the situation. She is the love of my life and helps me keep a healthy perspective on life. I want to thank my own parents Jose and Lea for their never-ending support and love. They are both the best parents I could ask for, and the best grandparents that my daughter could have. I'd like to thank my loving sister, Michelle, who recently moved to Providence and has been yet another source of support and warmth. I'm sad to leave her but happy we were able to spend the last few months in Providence together. Finally, my new family on Emily's side has always supported our decisions including our move to Rhode Island despite the distance between our current homes. I owe a big thank you to Lyndsey, Matt, Olivia, Reya, Nate, Danielle, Jude, Mary Beth, Roger, and Pat.

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CHAPTER 1

INTRODUCTION

Alcohol cue exposure effects have long been theorized as central motivating factors underlying problematic alcohol use. Consider two scenarios that illustrate these effects. First, imagine that a recovering alcoholic male, who has not had a drink in several months, walks past his favorite bar on his way home after the workday. He initially notices the bar sign outside and his attention is then drawn inside the bar. As he peers in through the windows, he sees a number of cues that signal alcohol consumption including bar stools, bottles, and alcohol itself. Suddenly his urge to drink becomes overwhelming. Despite remaining abstinent for several months, the man decides to enter the bar and he relapses. Now consider a second scenario in which an undergraduate college freshman female has spent three hours studying at the library for a midterm exam on the following day. As she begins to lose focus, she decides that she will benefit from a change of scenery and she leaves the library for her suite. When she returns to her suite, she finds that her suitemates and friends are playing drinking games. Even though her peers don't directly encourage her to drink, she gets an urge to join in on the fun upon the sight of her favorite beer bottle. She convinces herself that she can postpone her studying until the hours preceding her exam the next day. However, she ends up drinking more than planned, experiences hangover symptoms the next day and neglects her final study preparations. She ultimately does poorly on the exam and regrets her decision to drink.

Anecdotal evidence similar to these scenarios has led scientists and public health practitioners to consider the interplay of alcohol cue exposure, craving, and selective

attention, as a motivational force behind continuing alcohol use and relapse. Although these mechanisms have been extensively examined among adult populations of alcohol dependent drinkers like the relapsing alcoholic in the first scenario, less is known regarding how alcohol cues and internal mechanisms might contribute to underage drinking like the college student in the second scenario. Given the overall rates of alcohol use and increased risk to drink excessively among underage drinkers, there is a pressing need to improve our understanding of these determinants of drinking in this population. The present report examines the effects of alcohol cue exposure on underage drinkers' craving and attentional bias to alcohol.

Alcohol use as a problem among underage drinkers in the United States

Although drinking alcohol in the United States is illegal for people under the age of 21, people between the ages of 12-20 drink more than 10% of alcohol consumed in the country (Substance Abuse and Mental Health Services Administration [SAMHSA], 2007). Among this age group, alcohol is the most commonly used and abused drug ahead of tobacco and other illicit drugs. The implications of alcohol use among youth on public health can't be overstated. Alcohol has contributed to almost 5,000 injury deaths annually including the three leading causes of death for people under 21; traffic deaths, homicides, and suicides (U.S. Department of Health and Human Services, 2007). The totality of underage alcohol use harms cost the United States $24.6 billion in 2006 (Bouchery et al., 2011). Furthermore, earlier age of drinking onset is linked to greater likelihoods of later alcohol dependence (Dawson et al., 2008). Efforts to reduce excessive drinking among underage drinkers have both immediate and future societal benefits.

Patterns in underage drinking are best differentiated from adult drinking by comparing drinks consumed per drinking episode. Although the prevalence rates of drinking are not as high as those seen in adult populations, underage drinkers are much more likely to binge drink as defined by the consumption of five or more drinks in a single drinking episode (SAMHSA, 2007). Underage drinkers report drinking 4.9 standard drinks per drinking episode, as compared to 4.0 drinks per drinking episode among persons between 21-25, and 2.6 drinks per drinking episode for persons 26 and older (SAMSHA, 2007). It is not uncommon for underage drinkers to report amounts of alcohol consumption well over the minimum criteria for binge drinking. In 2009 and 2010, 11.7% of underage drinkers reported consuming nine or more drinks during their last drinking episode (SAMSHA, 2011). Furthermore, given the continuing development of adolescents, younger drinkers achieve higher Blood Alcohol Concentrations (BACs) with fewer drinks than adults (Donovan, 2009). These trends in underage drinking are reflected in the prevalence of alcohol use disorders (AUD) with 14.3% of 18- to 20-year-olds meeting criteria for alcohol dependence or abuse, the second highest rate of AUD status next to 21- to 24-year-olds. Even among younger underage drinkers between the ages of 15-17 years old, 7.5% meet criteria for either AUD.

Adolescence is a time characterized by rapid physical and neurobiological changes, which may result in age-related differences in the way that alcohol is subjectively experienced. In turn, these differences may contribute to the differing patterns of drinking behavior between underage and adult drinkers. Consistent with those drinking patterns observed in humans, animal models of alcohol use have demonstrated that adolescent rats may drink two to three times as much as their adult counterparts

(Brunell & Spear, 2005; Vetter, Doremus-Fitzwater, & Spear, 2007). Animal models have also shown that adolescents are less sensitive to alcohol's sedative effects and more sensitive to alcohol's effects on social facilitation (for review, see Spear & Varlinskaya, 2005). To the degree that sedative effects act as cues for the termination of a drinking episode, and social facilitation acts to promote alcohol consumption, the combination of these factors may partially account for underage drinker's increased likelihood to drink excessive amounts of alcohol.

To date, much of the research examining determinants of underage alcohol consumption has focused on external and social determinants including the influence of the home environment, peer groups, media and the legal drinking age. Research shows that youths with earlier ages of drinking onset are more likely to obtain alcohol at home (SAMSHA, 2011). Compared to parents who abstain from alcohol, parents who report heavy drinking occasions are twice as likely to have children who also have heavy drinking occasions and who meet criteria for alcohol dependence (SAMSHA, 2008). Peers influence underage drinking in a variety of ways including modeling, encouragement, and through misperceptions of how much other underage individuals drink (U.S. Department of Health and Human Services, 2007). The recent rise in peer use of social media also has an effect on alcohol use. Experimenter-generated Facebook pages that portrayed alcohol use as normative among older peers increased willingness to drink alcohol in adolescents between 13 and 15 years of age (Litt & Stock, 2011). Finally, some have proposed that the legal drinking age of 21 causes underage drinkers to drink in situations lacking parental supervision and thus prompting greater levels of

dangerous alcohol consumption, although there is a lack of consensus on this view (Hingson & White, 2012).

Successful clinical interventions and forms of prevention have been developed based on our understanding of these external determinants of underage drinking. For example, underage drinkers tend to overestimate peer rates and levels of alcohol consumption, and may drink in excess to conform to misperceived group norms. Interventions that informed underage drinkers of true peer consumption norms significantly reduced drinking with reductions lasting up to 16 months when feedback was delivered online (Moreira, Smith, & Foxcroft, 2009). Despite the considerable literature existing on external and social determinants of underage drinking, internal psychological and cognitive mechanisms thought to underlie problematic alcohol use are poorly understood in this population. There is reason to believe however, that internal mechanisms such as craving may also contribute to alcohol consumption among underage drinkers. Initial survey data from community-based youths suggest that craving is common among underage drinkers (Deas et al., 2001; 2005; Martin et al., 1995). Further, naltrexone has been shown to reduce both the likelihood of drinking and heavy drinking among underage drinkers between the ages of 15-19, while also attenuating craving in both the natural environment and the laboratory (Miranda et al., 2013). Results like these demonstrate that underage drinkers not only report craving, but also suggest that craving represents a viable target for intervention.

The conceptualization of craving in the addiction literature

Before a more elaborate discussion of craving for alcohol specifically among underage drinkers, it is important to understand how craving has been historically

defined, measured, and conceptualized as a causal mechanism for alcohol and other drug dependence. Despite the fact that craving is a central theoretical component to numerous models of addiction, there tends to be much debate surrounding this construct. Crucially, there is little agreement over a precise definition of craving given the subjective nature of the term. Generally speaking however, craving is agreed upon as a subjective motivational state (Shiffman, 2000) representing a wanting or desire for the target substance (Monti, Rohsenow, & Hutchison, 2000). Craving has also been conceptualized as an emotion to the extent that emotions function to prepare behavior (Baker, Morse, & Sherman, 1986; Franken, 2003; Shiffman, 2000). Analogous to the concept that fear is the emotion accompanying avoidance behavior, craving has been interpreted as the emotion accompanying approach behavior. A helpful analogy provided by Shiffman (2000) compares craving to hunger in that they are both subjectively experienced and signal a need for ingestion, and thus serve to motivate appetitive behavior. Finally, some theoretical models assert that craving includes cognitive components, such as Kavanagh's assertion that craving is characterized by intrusive and elaborated thoughts about appetitive targets (Kavanagh, Andrade, & May 2005). Similarly, some propose that craving may cause changes in cognition, for example biasing attention towards drug cues (Franken, 2003), which will be discussed in detail later in this chapter.

To further understand how craving is defined, it is imperative to review how craving is empirically assessed. Historically, subjective craving has been measured using single-item analog scales in which a drinker rates his or her level of craving, urge to drink, or desire to drink on an 11-point scale (0-10). Although single-item measures are quick and easy items to deliver making them desirable to minimize participant burden,

several well-validated multi-item questionnaires have been developed to assess craving as a multidimensional construct. For example, craving questionnaires include questions that assess urge to drink, expectations of positive effects following drinking, and ability to avoid alcohol when given the opportunity to drink (Bohn, Krahn, & Staehler, 1995). The most prevalent of these multi-item scales are the Alcohol Urge Questionnaire (AUQ; Bohn, Krahn, & Staehler, 1995), the Obsessive Compulsive Drinking Scale (OCDS; Anton, Moak, & Latham, 1995), the Alcohol Craving Questionnaire-Now (ACQ-Now; Singleton, Tiffany, & Henningfield, 2003) and the Penn Alcohol Craving Scale (Flannery, Volpicelli, & Pettinati, 1999). It is important to note that these scales differ with regards to whether they assess momentary craving (e.g., "What is your urge to drink right now?") or general craving experienced over greater periods of time (e.g., "How much of your time is occupied by ideas or images related to drinking?"). For example, the AUQ is a well-validated measure of momentary craving as users are asked to report on current levels of craving, whereas the OCDS is comprised of questions that assess the frequency of craving experienced over a specified timespan.

Craving as defined and understood among health care practitioners has also undergone recent changes. The DSM-V recently added a craving criterion to help diagnose alcohol use disorders (American Psychiatric Association, 2013) consistent with evidence from recent studies suggesting that a craving criterion helps differentiate individuals with and without alcohol use problems along an alcohol-use disorder continuum (Keyes et al., 2011). Whether or not craving may be used to differentiate individuals with varying levels of alcohol-related problems remains an open question however. As will be discussed in more detail later in the chapter, craving has been shown

to differentiate populations of drinkers on the basis of alcohol-related problems (Ihseen et al., 2011; Monti et al., 1987; Rohsenow et al., 1994), however this is not always the case, and craving for alcohol is commonly reported by less severe populations of social drinkers (Field, Mogg, & Bradley, 2005; Schulze & Jones, 2000).

Craving as a central construct among addiction theories

Craving may also be conceptualized through the lenses of numerous theories of drug use. The notion that craving for drug use may index problematic drug use is not a novel concept. In fact, many early theories and observations considered craving as *the* central and defining characteristic of addiction. Towards the end of the 18th century, Lettsom (1789) described alcoholics as needing alcohol in the same way that all humans need food, fueled by a desire for alcohol resistant to threats and persuasions. In the middle of the 20th century, as alcoholism was first conceptualized as a biological disease, craving still remained at the forefront of theory and was considered a marker of severe disease progression (Jellinek et al., 1955). Among the most extreme views, craving was thought of as the cause of alcoholism. More recent conceptualizations of addiction regard craving as a central construct while also incorporating other internal or external determinants of addictive behavior (Franken, 2003; Kavanagh, Andrade, & May, 2005; Ryan, 2002).

Many theories have conceptualized craving as a conditioned response to alcohol or other drug cues present in a user's environment. The logic follows basic principles of classical conditioning theory. With regards to alcohol use, each episode of alcohol administration can be thought of as a single conditioning trial. Alcohol itself represents an unconditioned stimulus (US), while the subjective and physiological effects of alcohol

represent unconditioned responses (URs). Cues or stimuli present at the time of alcohol administration become conditioned stimuli (CSs). Over time, these CSs may elicit conditioned responses (CR) even in the absence of alcohol consumption. The nature of these CRs is often a critical feature to differentiate models of addictive behavior, however craving is recognized as a CR in many theories. Among these conditioning theories, some posit that craving represents a desire to relieve withdrawal symptoms (Siegel, 1983; Wikler, 1948), whereas other theories posit that craving represents a wanting for the positively experienced subjective effects of drugs (Robinson & Berridge, 1993; Stewart, deWit & Eikelboom, 1984).

Conditioned withdrawal models

Wikler (1948) proposed one of the first theories of drug relapse grounded in conditioning theory. He asserted that neutral stimuli present at the time of drug withdrawal could eventually come to elicit conditioned responses after repeated presentations with withdrawal effects. He further described the conditioned responses as also resembling drug withdrawal. Therefore, conditioned withdrawal in the presence of conditioned stimuli was thought to cause relapse in addicts who become motivated to relieve the negative withdrawal symptoms. In this model, and expansions of this model (Drummond, Cooper, & Glautier, 1990), craving is viewed as one of the withdrawal symptoms, and thus conceptualized as a conditioned response. Drug consumption then, acts to relieve craving and thus negatively reinforces patterns of drug-seeking and consummatory behavior.

Siegel's conditioned compensatory response theory (1983) is a similar conditioning theory. Like Wikler (1948) and others, Siegel proposed that the

environmental cues present at the time of drug administration eventually elicit conditioned responses on their own. Siegel asserted that the set of these conditioned responses might help explain drug withdrawal and tolerance, but specifically he asserted that the CRs were opposite to the effects of the drug, and thus were labeled conditioned compensatory responses. For example, if consuming a drug (unconditioned stimulus) has the effect of increasing heart rate (unconditioned response), then over time, stimuli associated with this drug (conditioned stimuli) would engender decreases in heart rate (conditioned response) to compensate for the drug effect. This process can be used to explain both tolerance and withdrawal. When conditioned stimuli are present at the time of drug administration, they help to compensate the drug's effect, thus attenuating the effect and resulting in drug tolerance. Drug tolerance is evidenced by either a reduction in a drug's effect over time when dosage is held constant, or the requirement of progressive increases in drug dosage over time to achieve the desired effect. Withdrawal is thought to occur in this model, when exposed to conditioned stimuli while the drug is absent, resulting in the unpleasant experience of compensatory responses. Craving in this model results from the experience of negative withdrawal symptoms. As a result, drug use behavior is negatively reinforced when craving and withdrawal are alleviated.

Conditioned positive-incentive models

In contrast to negative reinforcement models of addiction, other conditioning models of craving assert that conditioned drug stimuli elicit conditioned responses in the form of neural states that mimic effects of the drugs themselves (Stewart, deWit, & Eikelboom, 1984). This results in an increased salience of the cues, which acts to increase the probability of drug-related thoughts and actions. Therefore, this view

proposes that continued drug use is not the product of a motivational state aimed to reduce withdrawal symptoms, but rather is motivated by the desire to experience the positive and rewarding drug effects. Craving in this sense represents this desire for the positive reinforcement effects.

Robinson and Berridge (1993) proposed a similar model of addictive behavior focused on principles of conditioning that describe neural changes in the brains of addicts. They asserted that repeated usage of addictive drugs in susceptible individuals eventually changes the user's neural circuitry such that brain circuits that regulate incentive salience attributed to stimuli become hypersensitive. In this sense, the brain cells and circuits of addicts attribute pathological levels of incentive salience to drugs and also drug-associated cues. The interaction between incentive salience mechanisms with associative learning mechanisms produces the focus on drugs among addicts. The learning mechanisms specify the object of desire, however the pathological motivation to compulsively use drugs is explained by the increase in incentive salience resulting from the sensitization of underlying brain circuits. The change in neural mechanisms of incentive salience may be manifested in behavior by either subjective craving or unconscious appetitive processes. Craving can persist in drug users, even if abstinent for years, due to the persistent changes in the incentive salience system in the brain. Given the emphasis of associative learning in the incentive-sensitization model, the presence of drug-related cues are important factors in an addict's environment and are capable of eliciting intense levels of craving.

Relationship between craving and drinking outcomes

The conditioning theories discussed thus far share two key empirically testable predictions. First, the theories posit that increases in craving motivate actual alcohol-seeking and consumption behavior. If true we should expect to find significant positive associations between reports of subjective craving and alcohol use. Despite the seemingly intuitive link between these constructs, the relationship between craving and alcohol use is a contentious topic in the field. This controversy is fueled by studies that show limited associations in craving predicting relapse among alcoholics, and also by human laboratory studies that report only modest correlations between craving and drinking outcomes (for review, see Tiffany & Conklin, 2000). Contrary to these modest findings, some studies have found stronger relationships between craving and drinking. These studies have found significant predictive relationships between craving and drinking in both treatment studies (Flannery et al., 2001; 2003; Oslin et al., 2009), and lab-based studies (Leeman, Corbin, & Fromme, 2009). Overall though, conflicting findings in the literature are problematic for these conditioning theories.

How can we account for these discrepancies in the alcohol literature? First, much of the research on alcohol craving has been hampered by methodological limitations. Only recently have well-validated multi-item measures been developed to overcome restricted measures of craving. Measures such as the OCDS (Anton, Moak, & Latham, 1995) and the AUQ (Bohn, Krahn, & Staehler, 1995) have been shown to significantly correlate with retrospective reports of drinking (r = +0.60, Anton, Moak, & Latham, 1996), and number of drinks consumed in a lab-based alcohol self-administration study (r = +0.65, O'Malley et al., 2002).

Another important consideration is that relapse studies frequently rely on retrospective reports of craving and drinking, which are subject to recall biases. Most of the research in which craving did not predict relapse is based on a lack of retrospective craving recall from participants who experience relapse (Tiffany & Conklin, 2000). However, motivational states including craving, have been proposed to be influential for behavior, although poorly encoded in memory (Loewenstein, 1996). Further, memories of alcohol use are also affected by the drug itself, with recollections of such events likely to be distorted (Weingarter et al., 1995). Various attributional biases and demand characteristics of the situation may also affect retrospective reports when drinkers are forced to explain determinants of drinking or relapse (Hammersley, 1994). Studies that reduce recall biases by measuring daily craving tend to show stronger relationships with drinking outcomes. For example, Oslin et al. (2009) recently studied the course of craving in adults with alcohol dependence during the first month of alcohol treatment. By collecting daily craving ratings, the investigators found that greater craving predicted lower abstinence rates.

An even more precise manner of reducing recall biases involves the use of ecological momentary assessment (EMA), which refers to real-time data collection in one's natural environment using modern technology such as palm-based computers or cell phones. This manner of data collection allows for a rich characterization of craving as it fluctuates over time and allows for temporally proximal comparisons of craving and actual drinking behavior. With regards to craving for alcohol, EMA studies have shown that heavy social drinkers frequently report craving as the basis for drinking on 41% of occasions (Collins et al., 1998). Litt, Cooney, and Morse (2000), used EMA methods to

characterize patterns of alcohol craving among recently treated alcoholics, and to track post-treatment drinking. The investigators found that the proportion of alcoholics' reports that included urges to drink significantly correlated with drinking days (r = +0.39) and heavy drinking days (r = +0.46). Furthermore, the mean levels of urge to drink in the field also strongly correlated with drinking days (r = +0.46) and heavy drinking days (r = +0.62).

Another critical issue amid this controversy is that studies examining the relationship between craving and alcohol use do not clearly define the hypothesized relationship on a conceptual level. Craving and alcohol use are measured with a number of different assessments, however differences between these assessments significantly affect the nature of one's research question. For example, researchers may consider a between-individual question, that is do people who crave more, also drink more? A separate analysis can be examined at a within-individual level, that is, do increases or fluctuations in craving predict subsequent drinking at the group level? These are separate questions with potentially separate answers, yet studies almost never delineate between these two levels and I assert that this lack of detail is a significant contributor to the controversy in the field. The implications regarding the answer to each question are also different.

The between-individual analysis is important to examine whether craving is unique to those that drink more or who have more alcohol-related problems and meet criteria for alcohol use disorders. If this is true, then craving should be more frequent and severe among those who drink more and experience more alcohol-related problems. The treatment implications would suggest that interventions that target craving would be more

effective for those with more problems. The within-individual analysis on the other hand, examines an important mechanistic question regarding fluctuations in craving. Conditioning theories make assumptions that cue exposure leads to increases in craving, which in turn motivates alcohol-seeking and consumption behaviors (Franken, 2003; Robinson & Berridge, 1993). In this sense, increases in craving within an individual act as a precursor to alcohol use. Studies that utilize global measures of craving and drinking do not measure this temporal relationship. If craving is indeed a precursor to alcohol consumption, then interventions that target reductions in craving should be effective more generally.

Alcohol cue reactivity

The second prediction shared by conditioning theories is that alcohol users will exhibit increases in craving when exposed to alcohol cues, although these theories differentially predict how craving is experienced. In the lab, the study of craving in response to alcohol cue exposure is commonly referred to as the 'cue reactivity' paradigm and has received considerable empirical attention (for review, see Carter & Tiffany, 1999). Alcohol-related stimuli are systematically presented in cue reactivity paradigms across a number of different modalities. Most commonly, alcohol cues are presented as pictorial, video, audio, *in vivo* (e.g., an actual mug of beer), and imaginal cues (e.g., vividly imagining past episodes of alcohol consumptions) (Conklin, 2006).

Whereas the relationship between craving and alcohol use remains contentious, there are a plethora of studies supporting the finding that exposure to alcohol cues results in increased reports of subjective craving (Carter & Tiffany, 1999). Carter and Tiffany (1999) conducted a seminal meta-analysis that included various types of cue reactivity

studies, and showed that alcoholics report increases in subjective craving when exposed to alcohol cues with a medium effect size (Cohen's d = +0.53). It should be noted however, that this effect size is smaller than cue reactivity effects on craving among smokers, cocaine addicts, and opiate addicts (range of d's = +1.18 to +1.29). Smaller but significant effects were also found in which alcoholics reported cue-induced increases in heart rate (d = +0.39), increased sweat gland activity (d = +0.33), and a nonsignificant decrease in skin temperature (d = -0.13). These effect sizes more closely resemble the overall effect sizes found across other combined addict groups with regards to heart rate (d = 0.26), sweat gland activity (d = 0.40), and skin temperature (d = -0.24).

The smaller subjective craving effect sizes among alcohol cue reactivity studies may be partially explained by the wide range of stimuli and beverage types involved with alcohol use. There is a smaller range of stimuli associated with smoking, cocaine and heroin use and many of these stimuli share common physical characteristics (e.g., physical similarity between cigarettes of different brands). The heterogeneous range of alcoholic beverages and associated stimuli (e.g., shot glass, beer bottle, wine glass) make it difficult to ensure that cue exposure paradigms will affect different alcohol users in a similar manner. It is even possible that alcoholics who prefer one type of drink may consider another type of drink to be an aversive stimulus. As a result, individualized stimulus sets are encouraged for cue reactivity procedures to ensure that individuals are exposed to stimuli relevant to their own drinking experiences. However, feasibility issues do not always make this possible and this design limitation may explain the smaller effect sizes found regarding subjective craving for alcohol.

In addition to subjective craving and physiological measures, alcohol cue reactivity studies have characterized other cue-elicited responses. Behavioral economic measures have shown that exposure to alcohol cues results in increases in the relative monetary value of alcohol (MacKillop et al., 2010). These measures include the hypothetical volume of alcohol consumption under conditions of zero cost, the price per drink at which alcohol consumption reduces to zero, and the maximum monetary expenditure that an individual would spend on alcohol in a single drinking episode. Studies have also utilized neuroimaging techniques to identify neural activation associated with alcohol cue exposure. These studies have demonstrated cue-elicited activation of brain regions including the ventral tegmental area, nucleus accumbens, amygdala, anterior cingulate cortex, dorsolateral prefrontal cortex, and the insula (Schacht et al., 2011; Tapert et al., 2004; Vollstädt-Klein et al., 2010).

It is often assumed in cue reactivity paradigms, that cue-elicited conditioned responses reflect a motivational state that contribute to continuing alcohol use as well as lapse and relapse for treatment-seeking individuals. Therefore, craving as assessed in cue reactivity paradigms has also been examined as a predictor of drinking outcomes and alcohol-related problems. Differences in craving response to cue reactivity paradigms have been found between alcoholic and nonalcoholic drinkers (Monti et al, 1987). Furthermore, when presented with visual alcohol cues, heavy drinkers show greater neural activation than light drinkers in brain circuits thought to underlie craving (Ihseen et al., 2011). Among abstaining alcoholics, some studies provide evidence that greater cue-elicited salivary responses and neural activation in the ventral putamen are predictive of relapse (Braus et al., 2001; Grusser et al., 2004; Rohsenow et al., 1994). However,

much like the controversy surrounding general craving and drinking outcomes, there is debate as to whether cue-elicited craving can predict relapse (Perkins, 2009). The extent to which methodological limitations account for this controversy is uncertain. There is an ongoing need for future research to characterize the relationship between cue-elicited responses and actual drinking outcomes.

Cognitive responses to alcohol cues

In addition to the conditioned responses discussed thus far, exposure to alcohol cues may also result in cognitive responses that motivate alcohol use. For example, one study found that exposure to alcohol cues slowed general reaction times among male alcoholics instructed to respond to tone presentations (Sayette et al., 1994). This was interpreted as initial evidence that alcohol cue exposure leads to an allocation of attentional resources onto alcohol cues, leaving fewer attentional resources available to respond to the tone presentations. Further, although not exposed to discrete alcohol cues, social drinkers tested in an alcohol-related context (simulated bar) were able to generate more alcohol-related sentences after receiving prime words than participants given the same task in a neutral context (Havermans et al., 2004). The authors concluded that alcohol context exposure improved the accessibility of alcohol-related memory associations.

A cognitive mechanism that has received considerable interest in the past decade is the study of attentional biases to alcohol cues among alcohol users (for review, see Field & Cox, 2008). Attentional biases to alcohol are most frequently measured in the lab using a modified version of the classic Stroop task (Stroop, 1935) and the visual probe task (for review, see Field, Schoenmakers, & Wiers, 2008). In the addiction Stroop

task, attentional biases to alcohol are indicated by slower color-naming reaction times for alcohol-related words compared to emotionally neutral words. In the visual probe task, an alcohol-related picture and matched control picture are simultaneously presented on a computer screen. When they disappear from the screen, a probe stimulus appears in the same location as one of the two prior stimuli. Faster reaction times to probe stimuli that replace alcohol-related pictures indicate an attentional bias to alcohol.

There is initial evidence to suggest that exposure to alcohol cues and contexts may result in an increased magnitude of attentional bias to alcohol. In one between-subjects study, heavy drinkers who completed the addiction Stroop task in an alcohol-related context showed a greater attentional bias towards alcohol-related cues than heavy drinkers tested in a neutral context and light drinkers tested in either context (Cox, Yeates, & Regan, 1999). Another study found that average weekly alcohol consumption positively correlated with attentional bias but only following *in vivo* alcohol cue exposure and not among participants in a control cue exposure condition (Cox, Brown, & Rowlands, 2003). Although this finding does not demonstrate that exposure to *in vivo* alcohol cues increases attentional bias, it does suggest that following cue exposure, stronger attentional biases may be observed in individuals who report greater alcohol consumption.

Attentional bias model (Franken, 2003)

Given these preliminary findings of cue exposure effects on attentional bias, one possible explanation is that cue exposure increases subjective craving, particularly for those who drink more, which in turn strengthens attentional biases to alcohol. This notion represents the core of the attentional bias model of drug use (Franken, 2003).

Franken's model resembles the incentive-sensitization theory (Robinson & Berridge, 1993) in that exposure to conditioned drug stimuli results in increases in dopamine in reward areas of the brain, which in turn orients attention towards the drug stimulus (2003). Attention in this model is described as a cognitive construct that allows humans' limited capacity of cognitive resources to focus on salient stimuli in preparation of approach and avoidance behaviors. Selective attention then, is the aspect of attention that facilitates processing of relevant stimuli and inhibits processing of less relevant stimuli. As attention becomes biased towards drug cues, the processing of these cues leads to subjective feelings of craving. The activation of craving further acts to strengthen the attentional bias resulting in a positive feedback loop thought to motivate drug use and relapse. In this model, attention and craving modulate each other, while each act as mediators between the effect of cue exposure on drug use.

Specifically, the attentional bias model of addiction (Franken, 2003) makes the prediction that alcohol craving positively correlates with attentional bias to alcohol. This model is partially supported by a meta-analysis that demonstrated a small but significant positive association between craving and attentional bias for alcohol cues ($r = +.19$, Field, Munafo, & Franken, 2009). Of particular interest, this meta-analysis found that this association was strengthened among studies that included manipulations to increase craving such as stress induction (Field & Powell, 2007) and delivering priming doses of alcohol (Schoenmakers, Wiers, & Field, 2008). Similarly, as predicted by the attentional bias model (Franken, 2003) alcohol cue exposure should enhance both craving and an attentional bias towards the cues themselves. As previously mentioned, initial findings suggest that attentional biases to alcohol are strengthened when in an alcohol-related

context (Cox, Yeates, & Regan, 1999). Despite this evidence, it remains unknown if the effects of alcohol contexts on attentional biases were mediated by craving, as it was not assessed in the study. To date, no study has assessed craving responses and changes in attentional bias following alcohol cue exposure.

Cognitive processing model (Tiffany, 1990)

In contrast to Franken's attentional bias model (2003), Tiffany's cognitive processing model (CPM) of addiction (1990) makes unique predictions regarding determinants of craving and its relationship to alcohol use. In an attempt to reconcile the conflicting findings regarding the relationship between craving and drug use outcomes, Tiffany proposed that drug use behaviors (1990), and specifically alcohol use behaviors (Tiffany & Conklin, 2000), are largely controlled by automatic cognitive processes. Similar to other behaviors that are frequently practiced, alcohol-seeking and consumption behaviors become automatic over time for heavy drinkers. As a result, the processes controlling these behaviors become very quick, require little focused effort, are difficult to control and are regulated largely outside of conscious awareness. Conversely, craving is conceptualized as a non-automatic process that is activated when automatized drinking behaviors are either voluntarily or involuntarily blocked. Craving in this sense requires mental effort and is limited by cognitive capacities. In this model, alcohol-seeking and consumption behaviors can occur in the absence of craving. Therefore, craving is not viewed as central to alcohol use, but rather serves as a marker of disrupted automatized processing. This may occur when either the automatized sequence of seeking and consumption behaviors is activated but some obstacle blocks the completion of the

sequence, or in the case of an abstinent alcoholic who is purposely attempting to prevent the sequence of automatized behaviors.

With regards to cue exposure, Tiffany's CPM makes the prediction that cues should activate the chain of automatized alcohol-seeking and consumption behaviors. Whether craving is experienced, is not a direct outcome of the cue exposure per se, but rather a product of whether or not there are obstacles impeding the chain of automatic behaviors. In the case of lab-based alcohol cue reactivity studies, if alcohol is unavailable for consumption during or immediately after cue exposure, Tiffany's CPM would predict increases in craving during cue reactivity. However, as a general rule, craving does not need to occur when automatized processes like attentional processing of alcohol cues are engaged.

Cue exposure effects and attentional bias among underage drinkers

Having reviewed alcohol cue exposure effects on craving and attentional bias in general, I will now specifically discuss relevant studies with underage drinkers. The previously mentioned conditioning models of alcohol use presume that craving for alcohol motivates drinking behavior and that craving develops as a conditioned response after repeated experiences with alcohol. However, none of these theories estimate how much experience is needed to develop conditioned responses to alcohol cues. It is important to understand the extent to which cue reactivity research findings among adults apply to underage drinkers who presumably have less drinking experience. We must also consider how age-related differences in drinking behavior may result in unique conditioning among underage drinkers. As compared to adults, underage patterns of less frequent but heavier drinking resemble spaced conditioning trials with presentations of a

stronger unconditioned stimulus (alcohol) and stronger unconditioned responses (alcohol's subjective and physiological effects). This schedule of trial spacing along with stimulus strength produces stronger conditioning historically (e.g., Barnet, Grahame, & Miller, 1995; Rescorla & Durlach, 1987), and suggests that underage drinkers may demonstrate robust conditioned responses that include considerable subjective craving.

Despite considerable research on craving among adults, our knowledge of craving during adolescence is based on only a handful of studies. Initial survey data from community-based youths suggest that craving is common in this age group (Deas et al., 2001; Deas, Roberts, & Grindlinger, 2005; Martin et al., 1995). These early findings were supported by several laboratory studies of alcohol cue reactivity in adolescent drinkers, with results showing stronger effects among underage drinkers with more alcohol-related problems. For example, Tapert and colleagues (2003) found that adolescents with AUDs exposed to alcohol pictures experienced greater neural activation in reward areas of the brain than non-AUD controls during a functional magnetic resonance imaging protocol. Others studied reactivity to *in vivo* alcohol cues and found that underage drinkers with alcohol dependence had greater cue-elicited craving compared to drinkers without an AUD (Thomas, Drobes, & Deas, 2005). A similar study found that photographs of alcohol elicited craving among community-based underage drinkers, with stronger reactions associated with heavier drinking histories (Curtin et al., 2005). On the whole, research suggests that underage drinkers crave alcohol when faced with drinking cues, and this effect appears more pronounced among those with greater alcohol problems.

Many of the studies that have assessed attentional biases to alcohol included college student samples with age ranges that overlap with underage drinkers in the United States (for review, see Field & Cox, 2008). However, much of this work has occurred outside of the U.S. where there are lower legal age limits for alcohol use. To the degree that problematic underage drinking patterns are influenced by the legal age limit, we must exhibit caution when generalizing these findings to underage drinkers in the U.S. With these limitations in mind, attentional biases to alcohol have been demonstrated among European college students who report a high level of alcohol-related problems and who report heavy drinking, but not for those who report few alcohol-related problems or who report light drinking (Field et al., 2004; Sharma, Albery, & Cook, 2001; Townshend & Duka, 2001). Also, the studies that demonstrated preliminary evidence of alcohol cue and context exposure effects on attentional biases were conducted with undergraduate students although the age range and mean age of these samples were not provided (Cox, Brown, & Rowlands, 2003; Cox, Yeates, & Regan, 1999). The combined findings suggest that college-aged drinkers have developed attentional biases to alcohol that may be predicted by rates of alcohol consumption or alcohol-related problems, and that attentional biases may be strengthened when in an alcohol-related context.

One final consideration is that the previously discussed theories were developed to explain addiction, or what we consider to be alcohol dependence among alcohol users. Although underage drinkers report problematic trends in their drinking behavior, these trends do not necessarily qualify an individual as meeting criteria for alcohol dependence. Although a subset of underage drinkers may indeed meet criteria for alcohol dependence, we cannot assume that theories of addictive behavior will thoroughly explain the

population's drinking behavior on the whole. This may partially account for the emphasis of studying external determinants of drinking among underage drinkers. While this work has clearly informed prevention strategies for this age group, research on the internal mechanisms that may also motivate problematic underage drinking have been understudied. Given that underage drinkers do report craving, especially in response to cue exposure, there is utility in testing theoretical predictions that posit internal mechanisms like craving and attentional bias as determinants of drinking. Further, adolescents undergo significant developmental changes in reward-related regions of the brain often associated with craving and attention. Crucially, connections from the prefrontal cortex (PFC) to the nucleus accumbens (NAc) continue to rise during adolescence with the percentage of these projection neurons that express D1 dopamine receptors peaking in adolescence (~40%) at far greater levels than observed at younger and older ages (4-5%) (Brenhouse et al., 2008). Indeed, dopamine release in the midbrain regions that include the NAc represents the neural mechanism underlying Franken's attentional bias model (2003). The potential implications of behavioral research on craving and attentional bias for prevention and intervention may be particularly important in this age group.

CHAPTER 2

EXPERIMENTAL OVERVIEW: AIMS & HYPOTHESES

Overview and aims

To briefly summarize, we know that underage drinkers exhibit problematic trends of increased binge drinking (SAMHSA, 2007). We also know that this population reports craving for alcohol (Deas et al., 2001; Deas, Roberts, & Grindlinger, 2005; Martin et al., 1995), and specifically reports increases in craving when exposed to alcohol cues (Curtin et al., 2005; Thomas, Drobes, & Deas, 2005). We are only beginning to understand the impact of craving among underage drinkers however, and the ability for alcohol cues to elicit craving. Additionally, the extent to which subjective craving is a determinant of drinking is poorly understood in this population of drinkers. Lastly, the effects of alcohol cue exposure on underage drinkers' cognitive responses have not been fully explored. Given the mounting interest of the relationship between craving and attention (Franken, 2003), there is a pressing need to examine these internal mechanisms that may contribute to underage drinking. Given these gaps in the literature, the following set of three studies includes these primary and secondary aims.

The first primary aim of the studies is to examine the relationship between real-time assessments of craving and subsequent drinking among underage drinkers. Specifically, these studies are designed to examine a within-individual question: Do individual increases in craving predict greater amounts of subsequent alcohol consumption? Experiment 1 utilizes EMA methods to avoid retrospective recall and global measures of craving and drinking when testing this relationship. As noted, recent real-time assessments of craving and laboratory procedures that permit drinking have

revealed stronger relationships between craving and subsequent drinking among adults (Leeman, Corbin, & Fromme, 2009; Litt, Cooney, & Morse, 2000; Oslin et al., 2009). These assessments have not yet been extended to an underage drinking population. Based on these findings and reports of craving among underage drinkers, I hypothesize that daily averages of craving will predict the volume of alcohol consumption in the same social day.

The second primary aim of the studies is to examine cue-elicited craving for alcohol in the natural environment and its relationship to cue-elicited craving in the laboratory. Although we know that underage drinkers exhibit enhanced craving in cue reactivity paradigms (Curtin et al., 2005; Thomas, Drobes, & Deas, 2005), little is known regarding responses to alcohol cues in the natural environment. The use of EMA also allows for the measurement of craving in response to the presence of alcohol cues in the natural environment, while also recording other situational variables that may impact craving including day of week, time of day, and peer presence. I hypothesize that alcohol cue reactivity effects would extend to the natural environment, in that underage drinkers would report a greater likelihood and intensity of craving in the presence of alcohol cues. I further hypothesize that lab-based cue reactivity paradigms will be ecologically valid models of this phenomenon, as evidenced by a significant predictive relationship between cue-elicited craving in the lab and cue-elicited craving in the natural environment.

The third primary aim of the studies is to examine the relationship between lab-based cue-elicited craving and attentional biases to alcohol cues. The second primary aim targets subjective craving as a cue-elicited conditioned response. This aim seeks to expand our knowledge on the basic phenomenology of cue reactivity by exploring

changes in attention as another potential response to alcohol cue exposure. Given the burgeoning focus of automatic cognitive processes underlying alcohol use, it is important to determine if such processes are state-specific as predicted by Franken's attentional bias model (2003). Experiments 2 and 3 include a measure to assess attentional bias to alcohol following various modifications of *in vivo* cue reactivity protocols. Consistent with the attentional bias model, I hypothesize that exposure to alcohol cues will strengthen subsequent attentional biases to alcohol, and that the relationship between craving and attentional bias will be positively associated whether the two constructs are expected to increase (Experiment 2) or decrease in magnitude (Experiment 3).

There are also two secondary aims of the studies. First, an overarching secondary aim of the studies is to replicate lab-based alcohol cue reactivity effects on craving among underage drinkers while providing measures of effect size to examine the robustness of this effect. As previously mentioned, alcohol cue reactivity has been previously observed in the lab with underage drinkers (Curtin et al., 2005; Thomas, Drobes, & Deas, 2005). Each of the following experiments contains a lab-based *in vivo* cue reactivity protocol and measures of subjective craving to add to this growing literature.

Finally, across all studies I aim to examine correlations between individual-level difference measures and the primary outcome measures: craving and attentional biases to alcohol. Although the primary aims are to examine craving and attentional biases to alcohol at the group level, all studies will also include a number of individual difference measures to assess alcohol-related problems and baseline rates of drinking. Given past findings regarding differences in both craving and attentional biases to alcohol between

individuals that differ based on alcohol-related problems (Sharma, Albery, & Cook, 2001; Thomas, Drobes, & Deas, 2005) and rates of alcohol consumption (Curtin et al., 2005; Field et al., 2004; Townshend & Duka, 2001), I predict similar positive correlations in the present set of studies. Although none of the studies will specifically recruit separate groups of heavy and light drinkers or individuals with and without alcohol use disorders, individual difference measures will provide continuous measures to explore potential correlations with craving and attentional bias to alcohol.

Study Implications

The aims of the project are of both theoretical and practical significance. From a theoretical standpoint, all of the following studies test the shared prediction that exposure to alcohol cues results in increased subjective craving (Franken, 2003; Robinson & Berridge, 1993; Siegel, 1983; Wikler, 1948). Evidence of cue-elicited craving would provide support for all theories predicting increases in craving when exposed to alcohol cues, but would not differentiate between withdrawal-related craving (Siegel, 1983; Wikler, 1948) or positively-reinforced craving (Robinson & Berridge, 1993; Stewart, deWit, & Eikelboom, 1984). These conditioning theories also assert that craving motivates actual drinking, and EMA data collected in Experiment 1 will examine craving's prospective relationship with drinking outcomes. Further, Experiments 2 and 3 are designed to specifically test Franken's attentional bias model (2003), in which both subjective craving and attentional biases to alcohol will be assessed following alcohol cue exposure. If craving significantly predicts attentional biases to alcohol, this would support the attentional bias model (Franken, 2003), however if the two are unrelated, this

would imply that craving does not necessarily occur in tandem with automatized alcohol-seeking processes (Tiffany, 1990).

Potential alcohol cue exposure effects on craving and attention carry important treatment implications as well. If alcohol cue exposure increases craving and attentional biases to cues, then this may help inform cue exposure treatments designed to decrease conditioned responses to cues. Traditionally, cue exposure treatments have been designed to attenuate craving in response to cues, but more recently, treatments have been developed to decrease attentional bias towards alcohol cues with preliminary findings demonstrating promising clinical outcomes findings (Fadardi & Cox, 2009; Schoenmakers et al., 2010). If craving is shown to mediate the relationship between cue exposure and attention, then treatments aimed to reduce craving may also be attenuating attentional bias to alcohol. If however, craving and attentional bias towards alcohol are not related, then the combination of attentional bias training with established methods of cue exposure therapy should be considered.

CHAPTER 3

EXPERIMENT 1: CRAVING FOR ALCOHOL IN THE NATURAL ENVRIONMENT AND IN THE LAB

In this study, lab and ecological momentary assessment (EMA) methods were paired to characterize the nature and function of alcohol craving in underage drinkers. Specifically, I tested whether alcohol cues elicit craving responses in underage drinkers under experimentally controlled conditions and, if so, whether this effect generalizes to the natural environment and prospectively predicts how much alcohol youths consume. I hypothesized that underage drinkers would show increases in craving and physiological arousal when exposed to *in vivo* alcohol cues compared to water cues in the lab, and that this effect would be more pronounced among underage drinkers with more severe alcohol-related problems. I expected this effect to generalize to the natural environment, such that underage drinkers would experience a greater likelihood and severity of craving when in the presence of alcohol cues in their daily lives compared to situations where alcohol cues are not present. I examined both the likelihood and severity of craving in the field because I anticipated infrequent reports of craving based on previous studies utilizing EMA methods to assess craving for alcohol among adults (Litt, Cooney, & Morse, 2000; Lukasiewicz et al., 2005). Similar to the lab portion of the study, I expected this effect would be more pronounced among underage drinkers with more severe alcohol-related problems. I also tested the hypothesis that higher daily averages of craving recorded in the natural environment would be associated with higher volumes of alcohol consumption on a given day. Finally, I examined the ecological validity of lab-based cue reactivity by testing the associations between craving in the lab and craving

and drinking recorded via EMA methods in the field. These associations have not been studied in underage drinkers and only one study examined these effects in adults and found modest correlations between craving recorded in the lab and craving in the field among adults in treatment for alcohol dependence (Litt, Cooney, & Morse, 2000).

Methods

Participants

Participants were 42 underage drinkers (ages 15-20 years) recruited from the community for a pharmacotherapy study on drinking and reactions to alcohol. Eligible participants consumed alcohol ≥ 2 times per week in the past 30 days and were able to read simple English for EMA purposes. Participants were excluded for the following reasons: prepubescent, history of alcohol treatment or treatment-seeking; opiate use in the past 30 days or opiate use disorder; positive toxicology screen for narcotics, amphetamines, sedative hypnotics, or opiates; clinically significant alcohol withdrawal; actively suicidal or psychotic; and medical conditions or medications that contraindicated taking the medication studied in the larger trial. Females were ineligible if they were pregnant, nursing, or unwilling to use birth control.

Procedures

The study was fully described to participants and, if younger than 18 years, to their parents. Consent was obtained from 18-20 year olds and from the parents of minors; assent was obtained from minors. Following screening, eligible participants completed a lab-based cue reactivity assessment followed by a premedication EMA period of approximately one week (M = 6.2 days; SD = 1.5), which constitutes the

assessment period for this study. No instructions were given to reduce or otherwise alter drinking behavior. The Brown University institutional review board approved this study.

Lab procedures. The cue reactivity (CR) protocol followed standard procedures (Miranda et al., 2008), which began with a 3-min acclimation period during which participants sat quietly. Acclimation was followed by a 3-min water cue trial, wherein participants were exposed to a glass of water accompanied by its commercially labeled bottle to control for exposure to a potable liquid. Participants then underwent a 3-min relaxation period followed by two consecutive 3-min alcohol cue trials. Two alcohol trials were administered to ensure a stable assessment of alcohol cue reactivity and were averaged together for analyses (Rohsenow et al., 2000). During alcohol cue exposure, participants were presented with a glass of their most commonly consumed alcoholic beverage accompanied by its commercially labeled bottle. The order of trials was not counterbalanced due to known carryover effects (Monti et al., 1987). During each trial, participants were instructed to hold and sniff the beverage for 5 seconds when auditory tones were presented. Thirteen tones were presented with variable intervals during each 3-min block to ensure all participants received equivalent olfactory exposure. Audio-recorded instructions afforded standardization across participants and observation through a one-way mirror ensured compliance. At the end of each 3-min period, participants rated their urge to drink on an 11-point Likert Scale. Physiological measures, which included mean arterial pressure (MAP) and heart rate measured in beats per minute (BPM), were continuously assessed during each 3-min period using a Criticare© Scholar II 507EP blood pressure monitor. All sessions took place in the afternoon or early evening on a participant's typical drinking day.

EMA procedures. Participants were taught to use the EMA program, which was implemented on handheld wireless devices (Omnia; Samsung Electronics, Ridgefield Park, NJ). Response options included visual analog bars (converted to discrete point scales), multiple checkboxes when more than one option was appropriate (e.g., activities), and categorical checkboxes when only one response was warranted (e.g., location). Other features enhanced the usability of the program, such as an alarm-clock feature, set by participants, to avoid assessments while sleeping. Data were transmitted wirelessly to the lab on a daily basis.

The EMA protocol lasted approximately one week (M = 6.2 days; SD = 1.5) for each participant. On each day, participants initiated momentary assessments upon waking (morning reports) and before and after consuming each alcoholic drink (drink reports). Participants also completed assessments in response to audible prompts (random assessments) delivered at randomly selected times once within each 3-hour block (e.g., 3 p.m. to 6 p.m.) throughout the day except when participants were sleeping or otherwise unable to respond to the device. This study focuses primarily on data collected during random assessments, with daily drinking levels culled from morning reports. Data from drink reports were excluded from the present study to avoid the confounding effects of alcohol intoxication and to best compare lab and field data.

Participants identified the presence of alcohol at random assessments by selecting one of three response options (not visible, visible directly [bottle, glass, etc.], or visible indirectly [television, advertisement, etc.]). Alcohol cues were dichotomized as not present versus directly or indirectly present. Contextual variables were also recorded to include as time-varying covariates in analyses. The EMA software date and time

stamped each entry. Each entry was dichotomized according to whether they were made on a weekend (6 p.m. on Friday through 6 p.m. on Sunday) to examine the influence of weekends on the dependent measures. Time of day was represented by four categories, with 6 p.m. to midnight serving as the reference category and the remaining categories representing exclusive 6-hr blocks. To control for whether entries were recorded on drinking days versus nondrinking days, each day was retrospectively dichotomized as a drinking (1) or nondrinking (0) day. Participants also indicated their location by selecting one of eight response options (home, friend's house, others' house, school, work, public place, vehicle, other location). Each option was coded as a binary variable indicating whether it was selected, with home serving as the reference category. Due to infrequent recordings in some locations, school and work were merged into one category and "others' house" was merged with the "other location" category. Participants also indicated who accompanied them at the time of each entry by selecting all applicable options from a menu (mother, father, brother, sister, child, other relative, boy/girlfriend, friend, teacher, other, no one). Participants were coded as being with peers (boy/girlfriend or friend), non-peers, or alone which served as the reference category.

Measures

Alcohol craving. Craving in the lab and field was assessed with the same single-item measure to allow for the most direct comparison of craving across settings. Participants rated their urge to drink on an 11-point visual analog scale from *no urge* (0) to *strongest ever* (10). This measure is widely used in lab and EMA research and was chosen to minimize participant burden in the field (Miranda et al., 2008; Ray et al., 2010).

Alcohol use. Baseline drinking was assessed using the 90-day timeline follow-back interview (TLFB; Sobell & Sobell, 1992). The TLFB was scored for the percentage of drinking days and heavy drinking days (>5 standard drinks for males, >4 standard drinks for females) in the last 90 days, and the number of standardized drinks per drinking day. Alcohol use during the monitoring period was assessed by EMA and the TLFB. EMA data obtained from the morning reports were the primary measure of drinking, with missing data culled from the TLFB. Morning reports included both the type of alcohol consumed and the volume reported in standard drinks, which served as the units for analyses.

Person-level variables. Demographic and clinical information was collected at baseline. For descriptive purposes, AUD diagnoses were derived using the Kiddie Schedule for Affective Disorders for School-Age Children (Kaufman et al., 1997). Interviewers received systematic training and achieved a high level of inter-rater reliability (kappa > 0.90) prior to conducting interviews independently. Diagnostic decisions were based on participants' reports and made by case consensus. Participants also completed the 23-item Rutgers Alcohol Problem Index (RAPI; White & Labouvie, 1989) to provide a continuous measure of alcohol problems used in analyses.

Data Analytic Strategy

Analyses were performed using the SPSS statistical package, version 20.0 (IBM, Armonk, NY). The hypotheses regarding cue reactivity in the lab were tested using generalized estimating equation (GEE) models to examine the main and interactive effects of cue type (water versus alcohol) and severity of alcohol-related problems (i.e., RAPI scores) on craving and physiological reactivity (BPM, MAP) while controlling for

age, sex, and baseline drinking levels. GEE models are essentially regression equations that account for the nesting of multiple observations within participants while controlling for autocorrelation (Zeger, Liang, & Albert, 1988). Several covariance structures were compared using the quasi-likelihood under the independence model criterion (Pan, 2001) to select the optimum working correlation matrix. Models for lab data used an autoregressive AR1 structure, assumed a normal link function, and coded cue type with an orthogonal contrast (− 0.5 for water cues versus 0.5 for alcohol cues). Continuous variables were standardized to ease interpretation of results; the model coefficients represent differences in standard deviation units associated with the predictors (effect size *d*).

The next set of analyses tested the hypothesis that alcohol cue exposure predicts craving among underage drinkers in the natural environment, and that this effect is more pronounced among participants with more severe alcohol-related problems. Analyses were restricted to random assessments recorded prior to drinking each day to eliminate the confounding effects of intoxication. Alcohol cue exposure was first tested as a predictor of the likelihood that participants experience craving. In this analysis, craving was categorized as a binary dependent variable (no craving = 0, any craving = 1). A separate model was then conducted to predict craving intensity. The dependent variable was the continuous measure of craving recorded during random assessments, which was transformed (logarithmically) due to positive skewness. In both models, an autoregressive AR1 structure best fit the data. A logit link function was used for binary outcome data and a normal link function was used when the dependent measure was continuous.

Both models examined the main and interactive effects of alcohol cue exposure (present vs. not present) and severity of alcohol-related problems (RAPI scores) on craving while controlling for person- (i.e., age, sex, baseline drinking levels) and occasion-level covariates (i.e., time of day, drinking day, weekend, social context, location). Cue type was coded with an orthogonal contrast (− 0.5 for water cues versus 0.5 for alcohol cues) and continuous variables were standardized. The likelihood and intensity of craving in response to alcohol cues in the lab were included in the respective models to examine whether lab-based cue reactivity predicted craving in the natural environment. The Bonferroni method controlled for inflation of Type I error by adjusting the threshold of significance ($\alpha = 0.05$) for each hypothesized effect on the likelihood and intensity of craving (Dar, Serlin, & Omer, 1994), yielding a modified threshold of significance ($\alpha = 0.025$).

The final set of analyses tested whether craving prospectively predicts alcohol use. First, craving recorded in the lab was examined as a predictor of the subsequent frequency and quantity of alcohol use in the field during the monitoring period. Specifically, this model tested the main and interactive effects of craving recording following alcohol-cue exposure in the lab and severity of alcohol-related problems on percent drinking days (frequency) and on the average number of standard drinks consumed each drinking day (quantity) in the natural environment while controlling for person-level covariates (i.e., craving recorded in response to the water-cue trial, age, sex, and baseline drinking levels). Models used an autoregressive AR1 structure and the Bonferroni method controlled for inflation of Type I error by adjusting the threshold of significance ($\alpha = 0.05$) for each hypothesized effect (modified $\alpha = 0.025$).

Daily average craving levels in the field were then tested to prospectively predict the volume of alcohol use each day. Days were sorted according to participants' individual social schedules (e.g., 8am to 3am) rather than calendar days. I examined the main and interactive effects of craving and severity of alcohol-related problems on drinking while controlling for person- (i.e., age, sex, baseline drinking levels) and occasion-level (weekend status) covariates. Other occasion-level covariates (i.e., time of day, social context, location) were not included due to an inability to compute meaningful daily summary scores given considerable within-day changes in these variables. Given the interest in person-level effects (i.e., how much an individual's drinking levels change in accordance with his or her craving level), within-person day-to-day variation in craving and drinking were disentangled from the effects of between-person variability in typical craving levels and drinking (Palta, 2003). Specifically, daily averages of craving recorded at random assessments (within-person effect) *and* each participant's average craving across the entire period (between-person effect) were both entered into the model. An unstructured covariance structure best fit the data and the model used a normal link function.

Results

Descriptive Analyses

Table 1 presents characteristics of the sample. All participants completed the lab CR protocol and contributed EMA data to the analyses. Physiological data were missing from one participant. Participants completed 85.6% of the random assessments ($N = 954$ reports), with an average of 22.7 (SD = 6.4) completed by each participant. Of these reports, 71 (8.2%) were recorded after drinking and thus excluded from analyses. An additional 18 (1.9%) were removed due to technological errors, leaving a total of 865 random assessments for analyses. As shown in Table 2, participants were more likely to report that alcohol was visible while at home ($\chi^2 = 6.12$, $p = .013$), on weekends ($\chi^2 = 4.81$, $p = .028$), in the evening (6pm – 5:59am; $\chi^2 = 4.61$, $p = .032$), and while with peers

Table 1. Baseline Participant Characteristics by Sex: Percentage or Mean (With Standard Deviation in Parentheses)

Variable	Males ($n = 20$)	Females (n = 22)	Overall ($N = 42$)
Age	18.4 (1.4)	18.6 (0.9)	18.5 (1.2)
Race			
Caucasian	75.0	72.7	73.8
African-American	5.0	13.6	9.5
American Indian	5.0	0.0	2.4
Asian/Pacific Islander	10.0	13.6	11.9
Hispanic[a]	25.0	9.1	16.7
Alcohol abuse	25.0	18.2	21.4
Alcohol dependent	50.0	54.5	52.4
RAPI	6.9 (6.3)	9.2 (8.7)	8.1 (7.6)
Cigarette Smoker	35.0	31.8	33.3
Drinking days[b]	27.2 (13.4)	28.5 (18.0)	27.9 (15.8)
Drinks per drinking day[b]	5.6 (3.6)	4.7 (3.8)	5.1 (3.7)
Heavy drinking days[b]	11.8 (9.1)	16.4 (20.4)	14.2 (16.0)

Note. [a] Ethnicity and race were not mutually exclusive; [b] Derived from the 90-day Timeline Follow-Back interview conducted at baseline; RAPI = Rutgers Alcohol Problem Index (higher scores indicate greater severity of alcohol-related problems)

($\chi^2 = 5.04$, $p = .025$). Alcohol was less likely visible in public locations ($\chi^2 = 15.52$, $p < .001$), in the morning (6am – 11:59am; $\chi^2 = 7.22$, $p = .007$), and while with others who were not peers ($\chi^2 = 8.01$, $p = .005$). In terms of drinking, participants consumed alcohol on 34.4% of study days, with an average of 4.88 (SD = 5.88) standard drinks per drinking day.

Table 2. Comparisons of Contextual Variables by Alcohol Cue Exposure in the Natural Environment

	Alcohol Cues					
	Not Visible (n = 677)		Visible (n = 188)			
Contextual Variable	*n*	%	*n*	%	χ^2	*p*
Time of day						
12 a.m. – 5:59 a.m.	35	5.2	18	9.6	4.96	.026
6 a.m. – 11:59 a.m.	146	21.6	24	12.8	7.22	.007
12 p.m. – 5:59 p.m.	262	38.7	65	34.6	1.07	.302
6 p.m. – 11:59 p.m.	234	34.6	81	43.1	4.61	.032
Drinking day	181	26.7	53	28.2	0.16	.691
Weekend	179	26.4	65	34.6	4.81	.028
Social context						
Peers present	273	40.3	93	49.5	5.04	.025
Nonpeers only	141	20.8	22	11.7	8.01	.005
Alone	263	38.8	73	38.8	0.00	.996
Location						
Friend's house	61	9.0	23	12.2	1.74	.187
School or work	93	13.7	21	11.2	0.85	.357
Public location	123	18.2	12	6.4	15.52	< .001
Vehicle	61	9.0	14	7.4	0.45	.500
Other location	55	8.1	20	10.6	1.18	.278
Home	284	41.9	98	52.1	6.18	.013

Note. Percentages are calculated within visibility category.

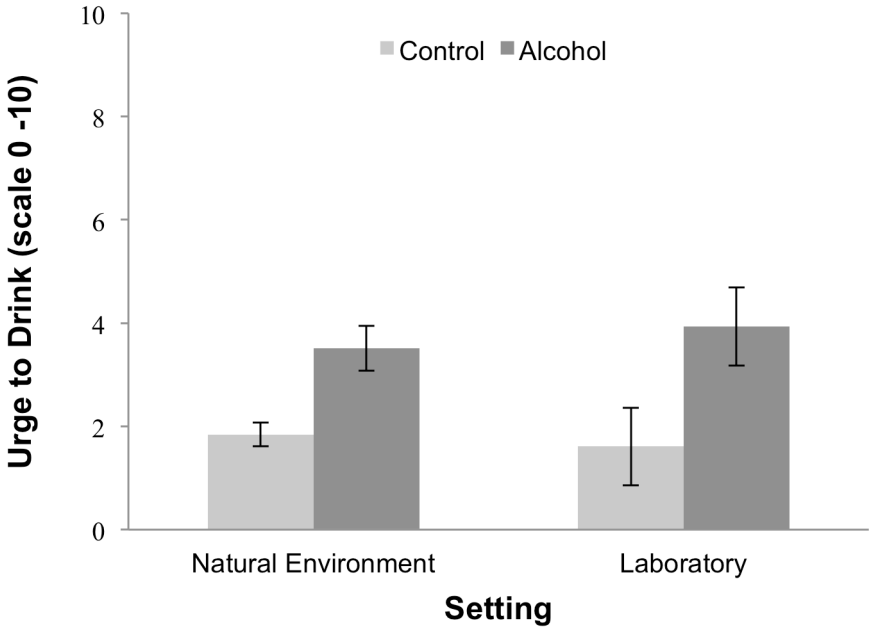

Figure 1. Comparison of cue-elicited craving reported in the natural environment and in the lab. 'Alcohol' bars refer to cases in which alcohol was reported as visible in the natural environment and trials involving *in vivo* alcohol cue exposure in the lab. 'Control' bars refer to cases in which alcohol was not visible in the natural environment and trials involving water cue exposure in the lab.

Effects of Alcohol Cues on Craving in the Laboratory

As shown in Table 3 and Figure 1, there was a main effect of cue type on craving ($\beta = 0.86$, 95% CI = 0.65 – 1.07, $p < .001$), such that alcohol cues increased craving relative to water cues, with a large magnitude effect size. Contrary to hypotheses, alcohol cue exposure did not affect BPM or MAP, and neither the main nor interactive effects of alcohol-problem severity predicted craving or physiological reactivity (all p's > .05). Baseline drinking rates ($\beta = 0.47$, 95% CI = 0.32 – 0.61, $p < .001$) and age ($\beta = -0.19$, 95% CI = -0.35, -0.03, $p = .017$) predicted craving such that participants with higher drinking levels and younger participants experienced greater craving.

Table 3. Summary of GEE Models Predicting Reactivity to Alcohol Cues in the Lab

	Dependent Measures Recorded in the Lab								
	Craving			Heart Rate (beats per minute)			Mean Arterial Pressure		
Predictor	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
Cue type	0.86	[0.65, 1.07]	< .001	− 0.04	[− 0.18, 0.10]	.581	0.18	[− 0.01, 0.36]	.066
RAPI	0.05	[− 0.13, 0.23]	.581	− 0.12	[− 0.48, 0.24]	.519	0.03	[− 0.25, 0.30]	.856
Cue Type × RAPI	0.16	[− 0.09, 0.41]	.204	0.08	[− 0.06, 0.22]	.252	0.05	[− 0.12, 0.21]	.583
Age	− 0.19	[− 0.35, − 0.03]	.017	0.17	[− 0.02, 0.35]	.073	0.26	[0.05, 0.47]	.017
Sex (female)	− 0.20	[− 0.59, 0.20]	.325	− 0.42	[− 1.02, 0.18]	.173	− 0.95	[− 1.49,− 0.41]	.001
Drinking days (%) [a]	0.47	[0.32, 0.61]	< .001	0.02	[− 0.26, 0.29]	.916	− 0.11	[− 0.44, 0.22]	.515

Note. Dependent measures are continuous and standardized. In all models, cue type was coded with an orthogonal contrast (− 0.5 for water cues versus 0.5 for alcohol cues). Continuous predictors were standardized prior to entry in all models; the reported coefficients represent standardized effects (effect size *d*). GEE = generalized estimating equation; RAPI = Rutgers Alcohol Problem Index (higher scores indicate greater severity of alcohol-related problems); CI = confidence interval; [a]derived from the 90-day Timeline Follow-Back interview conducted at baseline.

Table 4. Summary of GEE Models Predicting Momentary Craving From Alcohol Cues and Occasion- and Person-Level Covariates

	Dependent Measures					
	Likelihood of Craving [a]			Craving Intensity [b]		
Predictor	OR	95% CI	*p*	β	95% CI	*p*
Cue type	3.01	[1.80, 5.03]	<.001	0.42	[0.20, 0.64]	<.001
RAPI	2.09	[1.24, 3.51]	.005	0.26	[0.10, 0.42]	.002
Cue type× RAPI	2.11	[1.23, 3.62]	.007	0.25	[0.05, 0.46]	.015
Occasion-level covariates						
Time of day						
12 a.m. – 5:59 a.m.	0.81	[0.39, 1.72]	.589	− 0.14	[− 0.44, 0.16]	.361
6 a.m. – 11:59 a.m.	0.42	[0.24, 0.73]	.002	− 0.49	[− 0.67, − 0.30]	<.001
12 p.m. – 5:59 p.m.	0.75	[0.53, 1.06]	.101	− 0.22	[− 0.33, − 0.10]	<.001
6 p.m. – 11:59 p.m. (ref.)	1.00	[---- , ----]	----	0.00	[---- , ----]	----
Drinking day	1.98	[1.23, 3.07]	.003	0.21	[0.04, 0.38]	.014
Weekend	0.90	[0.64, 1.28]	.567	− 0.09	[− 0.23, 0.05]	.222
Social context						
Peers present	1.31	[0.87, 1.97]	.197	0.20	[0.05, 0.34]	.009
Nonpeers only	1.06	[0.61, 1.84]	.829	− 0.08	[− 0.24, 0.09]	.363
Alone (reference)	1.00	[---- , ----]	----	0.00	[---- , ----]	----
Location						
Friend’s house	1.05	[0.46, 2.38]	.909	0.14	[− 0.23, 0.51]	.462
School or Work	0.50	[0.32, 0.78]	.003	0.02	[− 0.21, 0.25]	.857
Public location	0.84	[0.57, 1.24]	.388	0.15	[0.01, 0.28]	.029
Vehicle	0.94	[0.59, 1.52]	.812	0.38	[0.13, 0.64]	.003
Other location	0.87	[0.52, 1.46]	.602	− 0.01	[− 0.18, 0.15]	.871
Home (reference)	1.00	[---- , ----]	----	0.00	[---- , ----]	----
Person-level covariates						

Table 4. (Continued)

Age	0.70	[0.42, 1.16]	.164	− 0.02	[− 0.20, 0.15]	.805
Sex (female)	0.87	[0.37, 2.03]	.742	− 0.12	[− 0.45, 0.22]	.486
Drinking days (%) [c]	0.66	[0.40, 1.08]	.097	− 0.15	[− 0.36, 0.06]	.152
Lab craving (alcohol cues)	2.93	[1.37, 6.23]	.005	0.31	[0.14, 0.48]	<.001

Note. Continuous predictors were standardized prior to entry in both models. In both models, cue type was coded with an orthogonal contrast (− 0.5 for assessments recorded when alcohol was not visible versus 0.5 for assessment recorded when alcohol was visible). GEE = generalized estimating equation; RAPI = Rutgers Alcohol Problem Index (higher scores indicate greater severity of alcohol-related problems); CI = confidence interval; [a] Binary outcome (0 when participants reported no urge to drink versus 1 when participants reported any urge to drink). [b] Continuous and standardized outcome; [c]Derived from the 90-day Timeline Follow-Back interview conducted at baseline; coefficients for craving intensity represent the standardized difference between situations when alcohol cue were visible versus not visible (effect size *d*).

Effects of Alcohol Cues on Craving in the Natural Environment

As hypothesized, there was a main effect of alcohol cue visibility on the likelihood of craving in the field (OR = 3.01, 95% CI = 1.80 – 5.03, $p < .001$), such that the presence of alcohol cues predicted a greater likelihood of craving (see Table 4). There was a main effect of alcohol problem severity (OR = 2.09, 95% CI = 1.24 – 3.51, $p = .005$), such that greater RAPI scores predicted higher likelihoods of craving. As expected, these main effects were subsumed under a significant Cue Type × RAPI interaction (OR = 2.11, 95% CI = 1.23 – 3.62, $p = .007$), such that adolescents with greater alcohol problems were more likely to experience craving in the presence of alcohol cues (see Table 4 and Figure 2).

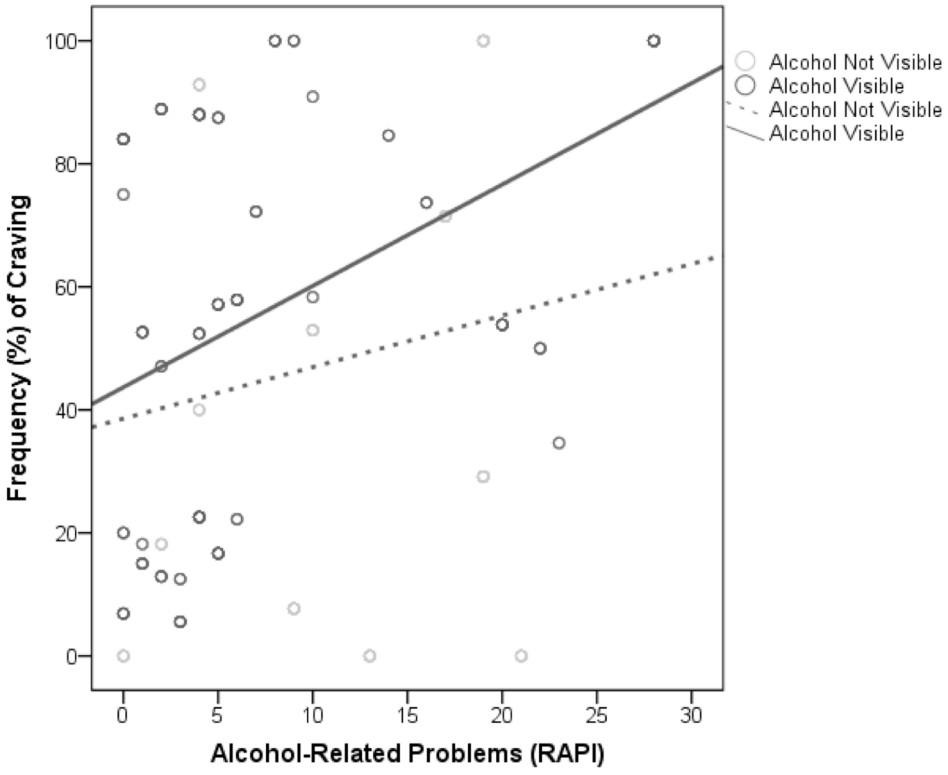

Figure 2. Observed frequencies of experiencing craving by individual measures of alcohol-related problems (RAPI) as a function of alcohol visibility in the natural environment. Best fitting lines for cases in which alcohol was visible or not visible are illustrated.

Results also revealed a main effect of alcohol cue visibility on the intensity of craving in the field (β = 0.42, 95% CI = 0.20 – 0.64, $p < .001$), such that participants reported higher levels of craving when in the presence of alcohol cues, with a medium magnitude effect size. There was a main effect of alcohol problem severity on craving intensity (β = 0.26, 95% CI = 0.10 – 0.42, $p = .002$), with those reporting more problems experiencing greater craving. As hypothesized, the Cue Type × RAPI interaction was also significant (β = 0.25, 95% CI = 0.05 – 0.46, $p = .015$), such that adolescents with more alcohol-related problems had higher levels of craving in the presence of alcohol cues (see Table 4 and Figure 3). Finally, both the likelihood and intensity of craving experienced in the lab predicted the likelihood (OR = 2.93, 95% CI = 1.37 – 6.23, $p = .005$) and intensity (β = 0.31, 95% CI = 0.14 – 0.48, $p < .001$) of craving in the natural environment, respectively (see Table 4).

Several occasion-level variables also predicted craving levels. Drinking days predicted greater likelihood (OR = 1.98, 95% CI = 1.23 – 3.07, $p = .003$) and intensity (β = 0.21, 95% CI = 0.04 – 0.38, $p = .014$) of craving. Time of day also influenced craving, such that participants were less likely to experience craving (OR = 0.42, 95% CI = 0.24 – 0.73, $p = .002$) during the morning (i.e., 6 a.m. to 11:59 a.m.), and when they did, it was less intense (β = -0.49, 95% CI = -0.67, -0.30, $p < .001$). A similar negative association between time of day and craving intensity was found for the hours between 12 p.m. and 5:59 p.m. (β = -0.22, 95% CI = -0.33, -0.10, $p < .001$). In terms of location, participants were less likely to experience craving while at school or work relative to home (OR =

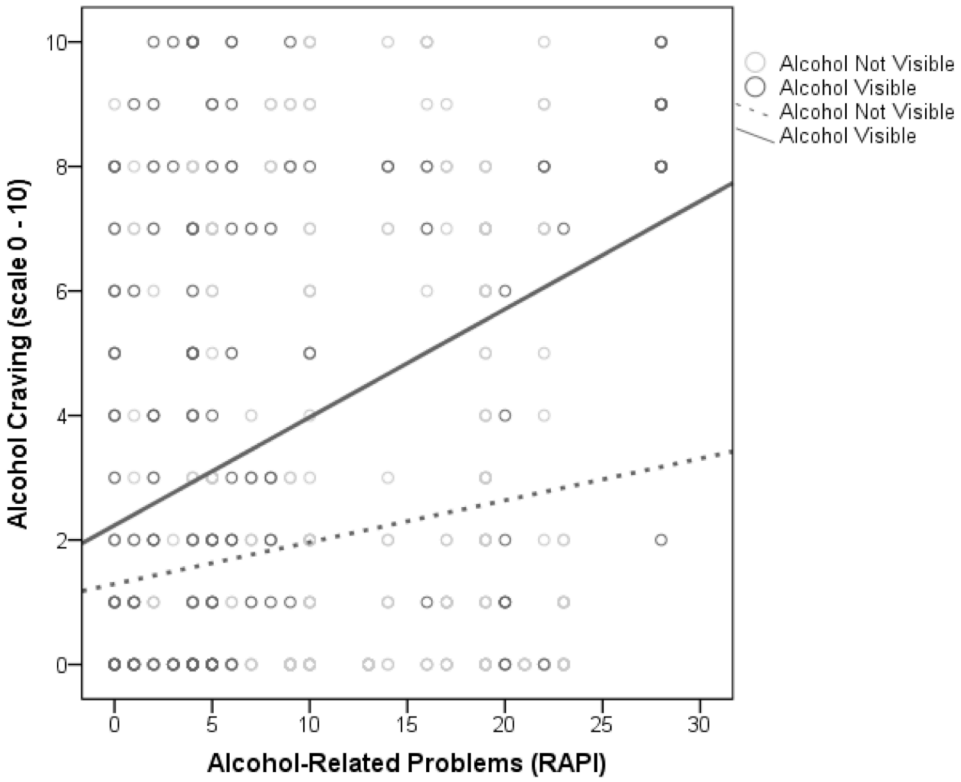

Figure 3. Observed intensities of craving (0-10 scale) from individual measures of alcohol-related problems (RAPI) as a function of alcohol visibility in the natural environment. Best fitting lines for cases in which alcohol was visible or not visible are illustrated.

0.50, 95% CI = 0.32 – 0.78, p = .003). Location influenced craving intensity as youths reported higher levels of craving while in a vehicle (β = 0.38, 95% CI = 0.13 – 0.64, p = .003) and in public locations (β = 0.15, 95% CI = 0.01 – 0.28, p = .029). Although the presence of peers did not influence the likelihood that participants experienced craving, it did predict more intense levels of craving (β = 0.20, 95% CI = 0.05 – 0.34, p = .009).

Effects of Craving on Drinking in the Natural Environment

As shown in Table 5, the main effects of craving in the lab on the frequency or quantity of drinking in the natural environment were not significant (p's > .05). The Craving × RAPI interaction was significant (β = 0.29, 95% CI = 0.04 – 0.54, p = .022),

Table 5. Summary of GEE Model Predicting Alcohol Consumption in the Natural Environment From Craving in the Lab

	Dependent Measures					
	Percent Drinking Days [a]			Average Drinks per Drinking Day [a]		
Model and Predictor	β	95% CI	*p*	β	95% CI	*p*
Craving (alcohol trials)	0.40	[− 0.05, 0.86]	.079	− 0.15	[− 0.52, 0.21]	.405
RAPI	0.21	[− 0.02, 0.44]	.073	0.19	[− 0.06, 0.44]	.146
Craving (alcohol trials) × RAPI	0.07	[− 0.14, 0.29]	.503	0.29	[0.04, 0.54]	.022
Person-level covariates						
Craving (water trial)	− 0.14	[− 0.57, 0.30]	.538	− 0.01	[− 0.39, 0.37]	.971
Age	0.20	[− 0.09, 0.49]	.181	− 0.27	[− 0.51, − 0.03]	.025
Sex (female)	− 0.08	[− 0.68, 0.52]	.795	− 0.25	[− 0.78, 0.28]	.363
Baseline percent drinking days [b]	− 0.08	[− 0.59, 0.44]	.766	-----	[---- , ----]	----
Baseline average drinks per day [b]	-----	[---- , -----]	----	0.12	[− 0.33, 0.57]	.600

Note. Continuous predictors were standardized prior to entry in both models. GEE = generalized estimating equation; RAPI = Rutgers Alcohol Problem Index (higher scores indicate greater severity of alcohol-related problems); CI = confidence interval; [a] Continuous and standardized outcome based on drinking behavior during the overall monitoring period; [b]Derived from the 90-day Timeline Follow-Back interview conducted at baseline; coefficients represent the standardized effects of predictors on drinking outcomes (effect size *d*).

however, such that greater craving during alcohol cue reactivity in the lab predicted higher average volumes of alcohol consumption in the natural environment among adolescents with more alcohol-related problems (see Figure 4). The Craving × RAPI interactive effect predicting the frequency of drinking (i.e. percent drinking days) was not significant ($p > .05$).

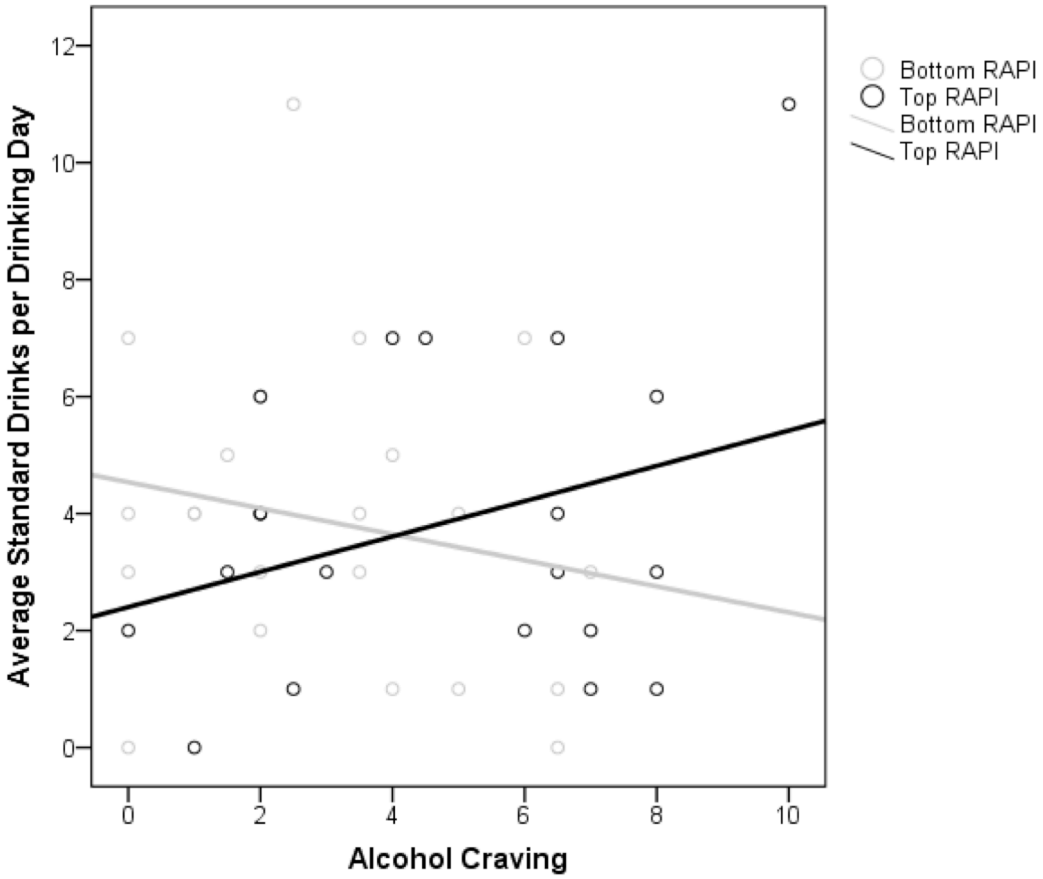

Figure 4. Observed intensities of craving (0-10 scale) from individual measures of alcohol-related problems (RAPI) as a function of craving following alcohol cue exposure in the lab. Best fitting lines for the 'Bottom' and 'Top' RAPI groups (median split used to distinguish groups) are illustrated.

As hypothesized and shown in Table 6, higher daily average craving levels predicted greater volumes of alcohol consumption (β = 0.34, 95% CI = 0.12 – 0.55, *p* =

.002). This finding reflects a within-subjects effect across the monitoring period and indicates that when adolescents experienced higher average levels of craving throughout the day they drink greater quantities of alcohol subsequently that day. Results also revealed a negative association between craving levels averaged across the monitoring period (i.e., between-subject effect) and the volume of alcohol consumption on a given day (β = -0.31, 95% CI = -0.51, -0.11, p = .002), however this relationship was only negative when daily average levels of craving were included in the model as the two craving variables were highly correlated resulting in a reversal paradox (Tu *et al.* 2008). As expected, severity of alcohol problems was positively predictive of alcohol consumption (β = 0.16, 95% CI = 0.03 – 0.29, p = .020).

Table 6. Summary of GEE Model Predicting Daily Volume of Alcohol Consumption From Craving in the Natural Environment and Occasion- and Person-Level Covariates

Predictor	β	95% CI	p
Daily average craving	0.34	[0.12, 0.55]	.002
Overall average craving	− 0.31	[− 0.51, − 0.11]	.002
RAPI	0.16	[0.03, 0.29]	.020
RAPI × Overall average craving	0.07	[− 0.12, 0.26]	.467
RAPI × Daily average craving	0.03	[− 0.22, 0.27]	.835
Occasion-level covariate			
Weekend	0.09	[− 0.15, 0.33]	.448
Person-level covariates			
Age	− 0.03	[− 0.09, 0.04]	.430
Sex (female)	− 0.16	[− 0.36, 0.04]	.119
Drinks per drinking day (Mean) [a]	0.08	[− 0.01, 0.18]	.075

Note. Continuous predictors were standardized prior to entry in both models. GEE = generalized estimating equation; RAPI = Rutgers Alcohol Problem Index (higher scores indicate greater severity of alcohol-related problems); CI = confidence interval; [a] Derived from the 90-day Timeline Follow-Back interview conducted at baseline; coefficients represent the standardized effects of predictors on drinking outcomes (effect size *d*).

Discussion

This study examined whether alcohol cues evoke craving among underage drinkers in the lab and in the natural environment, and tested the relevance of craving during this developmental period by examining the prospective association between craving and alcohol use. Lab results replicated previous findings that underage drinkers experience increases in craving when exposed to alcohol cues (Curtin et al., 2005; Thomas, Drobes, & Deas, 2005), with a large magnitude effect size (d = 0.86). In contrast, there was no effect of alcohol cue exposure on physiological reactivity among underage drinkers. Although there are modest effects of cue reactivity on physiological measures among adults (Carter & Tiffany, 1999), the current findings are consistent with previous work that found no effect of alcohol cue exposure on heart rate among adolescent alcoholics (Thomas, Drobes, & Deas, 2005). Of particular importance, this study extends lab-based research by demonstrating alcohol cues also predict craving among underage drinkers in their natural environment. Notably, this effect was robust (d = 0.42) even when controlling for occasion-level covariates (i.e., peer presence, weekend, etc.). These results provide support for the hypothesis that alcohol cues elicit craving among underage drinkers and indicate that the magnitude of this effect is comparable to those observed in adults (d = 0.53, Carter & Tiffany, 1999). The inclusion of lab and field data also allowed for a direct comparison of craving across settings. The ecological validity of lab-based cue reactivity paradigms was supported by the finding that the likelihood and intensity of craving experienced in the lab predicted the likelihood and intensity of craving experienced in the natural environment, respectively.

A central finding of this study was that severity of alcohol-related problems

moderated the effects of alcohol cues on craving in the natural environment. Specifically, alcohol cues were robust predictors of craving among participants with more severe pathological drinking habits but had negligible effects on craving among participants with few alcohol problems. Despite a similar pattern of results in the lab, the interaction between cue type and alcohol problem severity was not significant in the lab. It seems likely that the large number of repeated observations collected in the field afforded greater power to detect this moderating effect. Future lab research with larger samples is needed to clarify this possibility. Nonetheless, the observation that cue-induced craving in the natural environment is especially salient for underage drinkers further along the pathological drinking continuum supports the validity of craving as a clinically significant indicator of problematic drinking in this population.

The findings also showed that craving is clinically meaningful among underage drinkers by demonstrating that higher average daily craving levels were associated with higher volumes of subsequent alcohol use. This effect was upheld while controlling for between-participant differences in average craving across the monitoring period to ensure that a positive association between craving and drinking was not the product of heavier drinking participants who crave more in general. This finding is consistent with other demonstrations of positive associations between craving and drinking outcomes when measured in real time or on a daily basis (Leeman et al., 2009; Litt, Cooney, & Morse, 2000; Oslin et al., 2009). These findings build on existing research that typically tests associations between craving assessed at a single time point and drinking outcomes over extended monitoring periods (Bottlender & Soyka, 2004; Flannery et al., 2001; 2003) by using real-time assessments to examine prospective associations between daily variations

in craving and drinking behavior. Notably, craving recorded in the lab predicted how much alcohol participants consumed when they drank in the natural environment during the EMA monitoring period. This effect was only observed, however, among participants with greater alcohol-related problems. On the whole, these findings support the inclusion of craving as a clinically significant diagnostic indicator of alcohol addiction among underage drinkers. Moreover, these findings suggest that underage drinkers with alcohol problems may benefit from pharmacological and psychosocial treatments that target craving.

This study also showed that occasion-level variables other than alcohol cues predicted craving in the field. Namely, the presence of peers was associated with greater levels of craving intensity. Among nicotine craving studies, peers are sometimes conceptualized as distal cues that elicit craving similar to proximal cues among smokers (Conklin et al., 2013). In terms of alcohol, however, few studies have examined the potential of peers to influence craving. Peer selection and peer influences are generally explored more directly as determinants of drinking outcomes in adolescents (Ali & Dwyer, 2010; Mercken et al., 2012), with adolescents often imitating the drinking behavior of peers (Larsen et al., 2010). This study demonstrates the potential for peers to not only influence drinking directly, but also to influence craving.

Several considerations should be noted regarding the findings. Although field data afforded considerable statistical power to test within-subjects effects, the modest sample size limited the ability to explore between-subjects comparisons on potentially relevant variables, such as alcohol dependence. Replication in a larger sample with greater attention to individual difference characteristics is important. Similarly, the

modest sample size may have hindered the ability to detect cue effects on cardiovascular measures, as adult studies show such effects are small compared to subjective craving (Carter & Tiffany, 1999). Effect sizes for physiological measures in this study were similarly small. In addition, the current sample did not include treatment seekers. It remains unclear whether these findings extend to underage drinkers seeking treatment. Additional research is needed to clarify the impact of abstinence on craving and to assess whether the current findings are directly relevant to treatment providers. Finally, the study of craving in the field may have presented a self-selection problem in that, unlike cue exposure in the lab, the amount of alcohol cue exposure varied across participants. It is noteworthy, however, that cue effects in the field were robust even when controlling for person-level covariates.

On balance, this is the first study to test the effects of alcohol cues on craving among underage drinkers in the natural environment, as well as the first to prospectively examine the association between craving and future drinking in this age group. The findings implicate craving as an important clinical characteristic among underage drinkers and demonstrate the utility of pairing lab paradigms with EMA methods to better characterize reactivity to alcohol cues.

CHAPTER 4

EXPERIMENT 2: ALCOHOL CUE EXPOSURE EFFECTS ON CRAVING AND ATTENTIONAL BIAS

Experiment 1 demonstrated that momentary craving is a significant and positive predictor of subsequent drinking outcomes among underage drinkers, while also demonstrating cue-elicited increases in craving in both the lab and natural environment. Of critical importance to the ecological validity of lab-based paradigms, cue-elicited craving reported in the lab predicted cue-elicited craving reported in the natural environment. Experiment 2 aimed to utilize the lab-based procedure to examine other potential conditioned cognitive responses to alcohol-related cues. This study specifically tests Franken's attentional bias model (2003), which predicts that initial attention paid to alcohol cues results in increased craving, which in turn strengthens attentional biases to alcohol.

In this study, a within-subjects design was implemented to examine alcohol cue exposure effects on both craving and attentional bias among underage drinkers. Given the findings from Experiment 1, I hypothesized that the cue reactivity effect on craving would be replicated in this study. Also, given the tendency for non treatment-seeking college students to express an attentional bias towards alcohol cues presented for durations of 500ms or longer (Miller & Fillmore, 2010; Townshend & Duka, 2001), I hypothesized that underage drinkers would exhibit strengthened attentional bias to alcohol if craving is elevated after alcohol cue exposure. Consistent with Franken's attentional bias model (2003) and previous research (Field, Munafo, & Franken, 2009), I hypothesized that craving would positively predict attentional biases to alcohol assessed

immediately after alcohol cue reactivity when craving was expected to be relatively high. I similarly predicted that craving would mediate the relationship between cue type and attentional bias as evidenced by within-subject differences in craving across sessions (alcohol cues vs. water cues) positively predicting within-subject changes in attentional biases across sessions (Judd, Kenny, & McClelland, 2001). Lastly, I explored potential changes in the strength of craving for alcohol within-session as a function of repeated, nonreinforced presentations of alcohol stimuli, which could result in the extinction of a conditioned response.

Method

Participants

Undergraduate students were invited to participate in the study as an opportunity to fulfill course requirements. Students, 18 to 20 years of age, were eligible to participate if they drank at least one beer on a weekly basis over the past month. Individuals were considered ineligible if currently seeking treatment for alcohol problems or if having received treatment in the past 30 days.

Procedure

The basic study design is outlined in Figure 5. Participants completed two sessions separated by at least one week, and occurring at the same time of day. In each session, participants completed the cue reactivity protocol followed by a visual probe task to assess attentional bias towards alcohol. The primary difference between each session was the type of cue presented during cue reactivity procedures with participants receiving

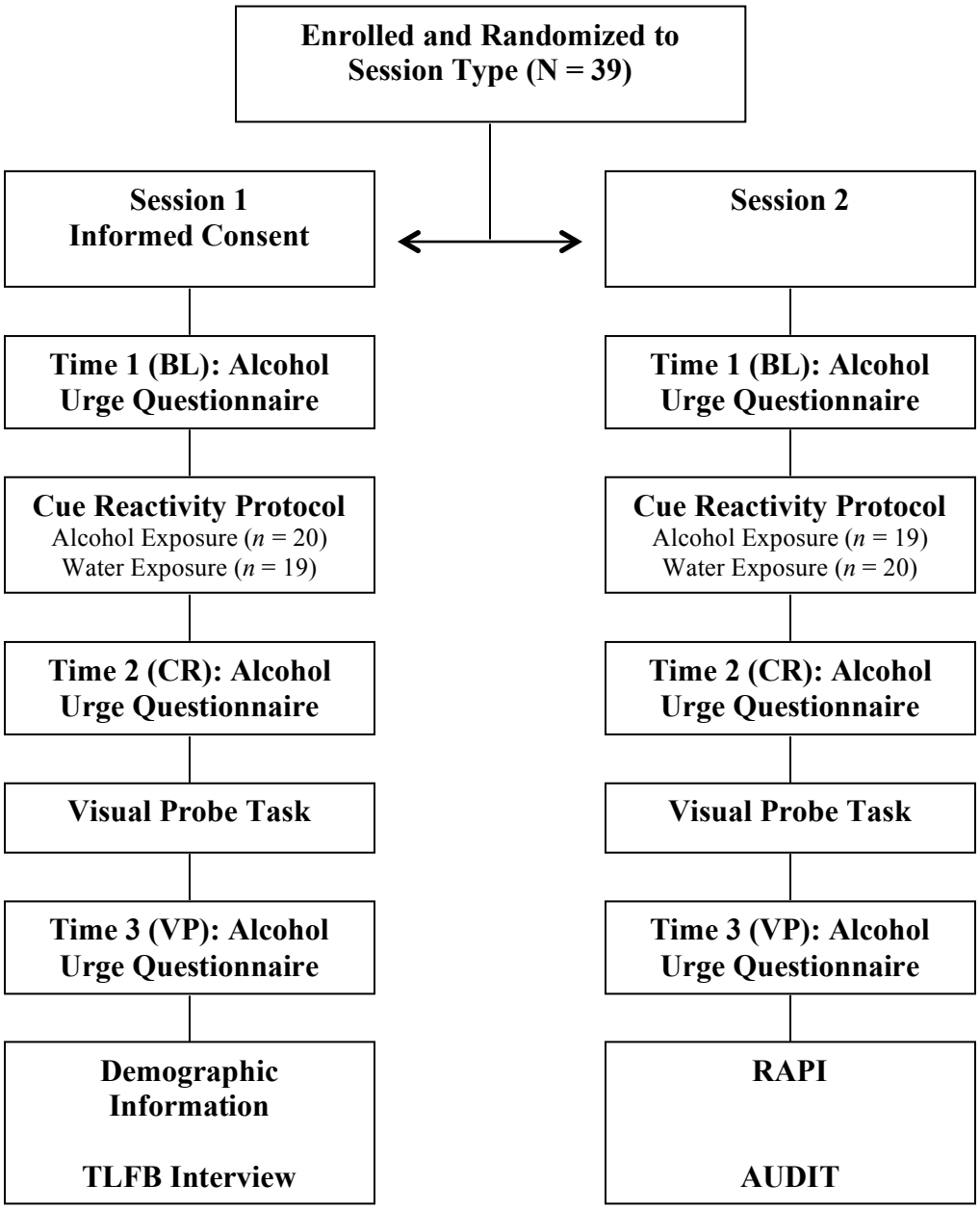

Figure 5. Flowchart illustrating basic design for study. Participants completed two separate sessions at least a week apart that differed on the basis of cue type during the cue reactivity protocol, and on the individual difference measures administered at the end of each session. Participants received alcohol cue exposure in one session and received water cue exposure in the other session in a counterbalanced order. BL = collected at Baseline, CR = collected after Cue Reactivity, VP = collected after Visual Probe, TLFB = Timeline Follow-Back, RAPI = Rutgers Alcohol Problem Index, AUDIT = Alcohol Use Disorders Identification Test

alcohol exposure for one session, and receiving water exposure for the other session in a counterbalanced order. In each session, visual probe tasks included the same stimuli and were always delivered immediately after cue reactivity procedures. Additional individual difference measures were collected after the final visual probe task due to the concern that the nature of these assessments (e.g., recalling drinking episodes) might affect craving and attentional bias to alcohol. All participants signed informed consent before beginning the study. The Brown University institutional review board approved this study.

Cue Reactivity (CR). The CR procedure followed well-established procedures with modifications made to separate alcohol and water cue exposure across sessions (e.g., Monti et al., 1987, 2001). Participants were asked to abstain from drinking the morning of the study and prior to starting, participants were breath-tested to ensure a Blood Alcohol Content (BAC) of 0.00 (all participants had a BAC of 0.00). Participants then received standardized instructions about the cue reactivity assessments while becoming acclimated to the laboratory. Prior to cue exposure, participants indicated which one of three beer options they most commonly drink and whether they were more likely to drink that beer from a cup or glass. The three beer options represented the spectrum of beer choices popular among college student drinkers and covered the beer preferences of the study participants.

Sessions began with a 3-minute relaxation block, in which participants sat quietly and did nothing. In one session, participants were instructed to hold and smell a glass of water for 3 minutes to control for exposure to a potable liquid. In the other session, participants were instructed to hold and smell a cup or glass of beer for 3 minutes, with

the type of beer and container matching that which the participant indicated as having the most experience with outside of the lab. The order of cue type presented in the first session was counterbalanced across participants with half receiving water first, and the other half receiving alcohol first. The participants then completed an additional and identical 3-minute block in which they held and smelled a new cup or glass of the same beverage from earlier in the session. Participants were asked to smell the beverage for 5 seconds each time a tone sounded with 13 tones delivered during each 3-minute block with variable intervals to ensure that all received the same olfactory exposure. Following each 3-minute block, participants completed measures of subjective craving. Craving reported after the relaxation block represents the baseline measure of craving, whereas craving reported after the final block of cue exposure represents the cue reactivity measure of craving. Compliance was monitored by observation through a one-way mirror and all participants complied with the study protocol.

Visual Probe. Immediately following completion of the cue reactivity procedure in each session, participants completed a visual probe task to assess attentional bias to alcohol cues. The task stimuli have been used in previous work evidencing robust attentional bias effects (Miller & Fillmore, 2010) and consisted of ten alcohol-related pictorial stimuli matched with ten neutral pictorial stimuli. Each alcohol picture depicted a solitary alcoholic beverage and was matched with a neutral picture consisting of a non-alcoholic drink of a similar size (e.g., a can of beer matched with a can of soda). There was no difference in the visual probe task procedure between sessions. Participants were seated in front of a laptop computer and instructed to identify the location of a single probe stimulus, which always followed the presentation of a pair of pictorial stimuli. The

task began with six practice trials, in which neutral picture pairs were presented. Following a short break, two buffer trials were presented with neutral pairs again, followed by 80 critical trials, in which alcohol-control picture pairs were presented. Each trial began with a fixation cross presented in the center of the screen for 500 ms, immediately followed by the bilateral presentation of a picture pair for 1000 ms, with pictures positioned to the left and right of the previously presented fixation cross. After picture offset, a visual probe stimulus was presented on either the left or right side of the screen where the picture stimulus was presented. The visual probe stimulus was an "X" presented in red font, and the presentation of the probe stimulus required the participant to press one of two response keys ("A" for left and "L" for right) on the keyboard indicating on which side the probe appeared. After making a response, there was an intertrial interval of 500 ms before the next fixation cross appeared. Throughout the 80 critical trials, each alcohol-control picture pair was presented eight times, with the alcohol-related picture being presented four times on the left and four times on the right of the screen. Probes replaced alcohol-related and neutral pictures with equal frequency, and appeared on each side of the screen with equal frequency. Attentional bias to alcohol was indicated by shorter (i.e., faster) reaction times to probes replacing alcohol-related pictures than to those replacing neutral pictures. Following completion of the visual probe task, participants rated their urge to drink to assess post-task levels of craving.

Measures

Alcohol craving. Participants completed the Alcohol Urge Questionnaire (AUQ; Bohn, Krahn & Staehler, 1995), an 8-item measure of momentary craving with items

rated on a scale from 1 to 7, with total scores on the questionnaire ranging from 8 to 56 and higher scores representing greater momentary craving.

Alcohol use. Baseline (pre-study) drinking levels were assessed using the 90-day timeline follow-back interview (TLFB; Sobell & Sobell, 1992). The TLFB was scored for the percentage of drinking days and heavy drinking days (>5 standard drinks for males, >4 standard drinks for females) in the last 90 days, and the number of standardized drinks per drinking day. Two separate measures assessed alcohol use and alcohol-related problems. First, participants completed the Rutgers Alcohol Problem Index (RAPI; White & Labouvie, 1989); a 23-item measure for assessing adolescent problem drinking and negative consequences that result from drinking including problems at school/work, interpersonal difficulties, emotional troubles, and signs of tolerance. Items were rated on a scale of '0 = never' to '4 = more than 10 times.' Norms have been established on adolescent communities and treatment samples (12 to 21 years old), which allows for comparisons of problem drinking score on an individualized basis. Second, the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001) was administered to gauge hazardous and harmful patterns of alcohol use. The AUDIT consists of 10 short questions based on three domains; hazardous alcohol use, dependence symptoms, and harmful alcohol use. The items were also rated on likert-type 0-4 scales with a total possible score of 40, although scores above 8 indicate hazardous patterns of drinking (Babor et al., 2001).

Data Analysis

Craving for alcohol. To examine the effects of cue reactivity and other potential changes in craving throughout each session, the AUQ was delivered at three time points: just after the relaxation period of the cue reactivity procedure (Time 1: Baseline), after cue reactivity which immediately preceded visual probe task performance (Time 2: CR), and immediately after completing the visual probe task (Time 3: VP). Summary AUQ scores were used as the measure of craving in all analyses. Craving was analyzed using a repeated measures analysis of variance (ANOVA) with Time (Time 1, Time 2, Time 3) and Session (Alcohol vs. Water) as the within-subjects factors. Craving was also compared in a series of Bonferroni corrected t-tests ($\alpha = 0.0125$) between these time points to assess the impact of initial cue reactivity on craving (Time 1 and Time 2), and potential changes in craving following completion of the visual probe task (Time 2 and Time 3) in each session. All reported effect sizes (Cohen's *d*'s) take into account the correlation between means as suggested by Morris and DeShon (2002) to correct for dependence between means in within-subjects designs.

Attentional bias. For the visual probe task, trials with errors (incorrect identification of probe side) were removed (1.6%) and median reaction times were determined for each participant's responses to probes that replaced alcohol cues and probes that replaced neutral cues. Median scores were used due to positive skewness among the reaction times, although the same pattern of results was obtained using trimmed mean scores. To test the hypothesis that alcohol cue exposure biases attention towards alcohol cues, median reaction times were analyzed using a repeated measures ANOVA with Trial (Alcohol Cue vs. Neutral Cue) and Session (Alcohol vs. Water) as within-subject factors. To examine if participants were exhibiting an attentional bias

towards alcohol cues in either session, separate post-hoc, Bonferroni corrected *t*-tests ($\alpha = 0.025$) were run to compare reaction times to alcohol and neutral cue trials separately for the alcohol and water sessions.

Craving and attentional bias. A series of regression analyses were conducted to examine the relationship between craving and attention. Specifically, craving scores measured after cue reactivity in each session were used in separate linear regression models to predict attentional bias towards alcohol in the same session. Finally, within-subject changes in craving scores across sessions were used to predict within-subject changes in attentional biases across sessions as recommended to test for within-subjects mediation (Judd, Kenny, & McClelland, 2001).

Table 7
Baseline Participant Characteristics by Sex: Percentage or Mean (With Standard Deviation in Parentheses)

Variable	Males ($n = 20$)	Females (n = 19)	Overall ($N = 39$)
Age	19.2 (0.8)	19.0 (0.8)	19.1 (0.8)
Race[a]			
Caucasian	65.0	78.9	71.8
African-American	20.0	0.0	10.3
Hispanic	10.0	15.8	12.8
Asian	20.0	15.8	18.0
Native Hawaiian/Pacific Islander	0.0	5.3	2.6
American Indian/Native Alaskan	5.0	0.0	2.6
RAPI	11.4 (9.3)[1]	6.3 (5.6)[1]	8.9 (8.0)
AUDIT	13.7 (5.3)[2]	10.4 (4.5)[2]	12.1 (5.1)
Percent Drinking Days[b]	36.7 (17.5)[3]	24.5 (10.0)[3]	30.8 (15.4)
Percent Heavy Drinking Days[b]	22.1 (14.7)[4]	9.1 (8.2)[4]	15.8 (13.5)
Drinks Per Drinking Day[b]	6.3 (2.5)[5]	4.1 (2.0)[5]	5.2 (2.5)

Note. [a] Races were not considered mutually exclusive [b] Derived from the 90-day Timeline Follow-Back interview conducted at baseline; [1] $t(37) = 2.06$, $p = .047$. [2] $t(37) = 2.12$, $p = .041$. [3] $t(37) = 2.67$, $p = .011$. [4] $t(37) = 3.40$, $p = .002$. [5] $t(37) = 3.00$, $p = .005$. AUDIT = Alcohol Use Disorders Identification Test; RAPI = Rutgers Alcohol Problem Index

Results

Descriptives and bivariate correlations. Table 7 shows descriptive information for the sample separated by gender. There were no gender differences with regards to age in the sample. However, males reported more alcohol problems as measured by both RAPI ($t(37) = 2.06$, $p = .047$) and AUDIT scores ($t(37) = 2.12$, $p = .041$), and reported more drinking days ($t(37) = 2.67$, $p = .011$), heavy drinking days ($t(37) = 3.40$, $p = .002$) and drinks per drinking day ($t(37) = 3.00$, $p = .005$) in the past 90 days prior to study enrollment. Bivariate correlations among individual predictor variables and the main outcome variables are presented in Table 8. Significant correlations were present between all measures of alcohol problems and measures of baseline alcohol use (all p's <

Table 8
Correlation Matrix for Study Outcome and Predictor Variables

Measure	1	2	3	4	5	6	7	8
1. Craving (A)	----							
2. Craving (W)	.20	----						
3. Attentional Bias (A)	.27	.01	----					
4. Attentional Bias (W)	−.07	−.14	.14	----				
5. RAPI	.24	.14	.19	−.25	----			
6. AUDIT	.21	.13	.06	−.36*	.71**	----		
7. Drinking Days (%)[a]	−.01	.06	.06	−.08	.36*	.40*	----	
8. Drinks Per Drink Day[a]	.01	.04	−.17	−.29	.41*	.75**	.26	----

Note. (A) = Assessed during alcohol sessions; (W) = Assessed during water sessions; Craving reflects subjective ratings scored during cue reactivity and prior to the visual probe task. Attentional bias reflects the bias of median reaction times during visual probe task; RAPI = Rutgers Alcohol Problem Index (higher scores indicate greater severity of alcohol-related problems); AUDIT = Alcohol Use Disorders Identification Test (higher scores indicate greater severity of alcohol-related problems); [a]derived from the 90-day Timeline Follow-Back interview conducted during first session; *$p < .05$, **$p < .01$.

.05). None of the individual-level predictors had significant correlations with measures of craving or attention with the exception of AUDIT scores, which negatively correlated with attentional bias to alcohol cues but only during the water session (r = -.36, p < .05).

Craving for alcohol. Figure 6 presents mean levels of subjective craving (AUQ scores) measured at the three time points separated by each session type. A repeated measures ANOVA revealed main effects of Time (F(1,38) = 18.58, p < .001) and Session (F(1,38) = 17.53, p < .001) subsumed under a Time x Session interaction (F(1,38) =

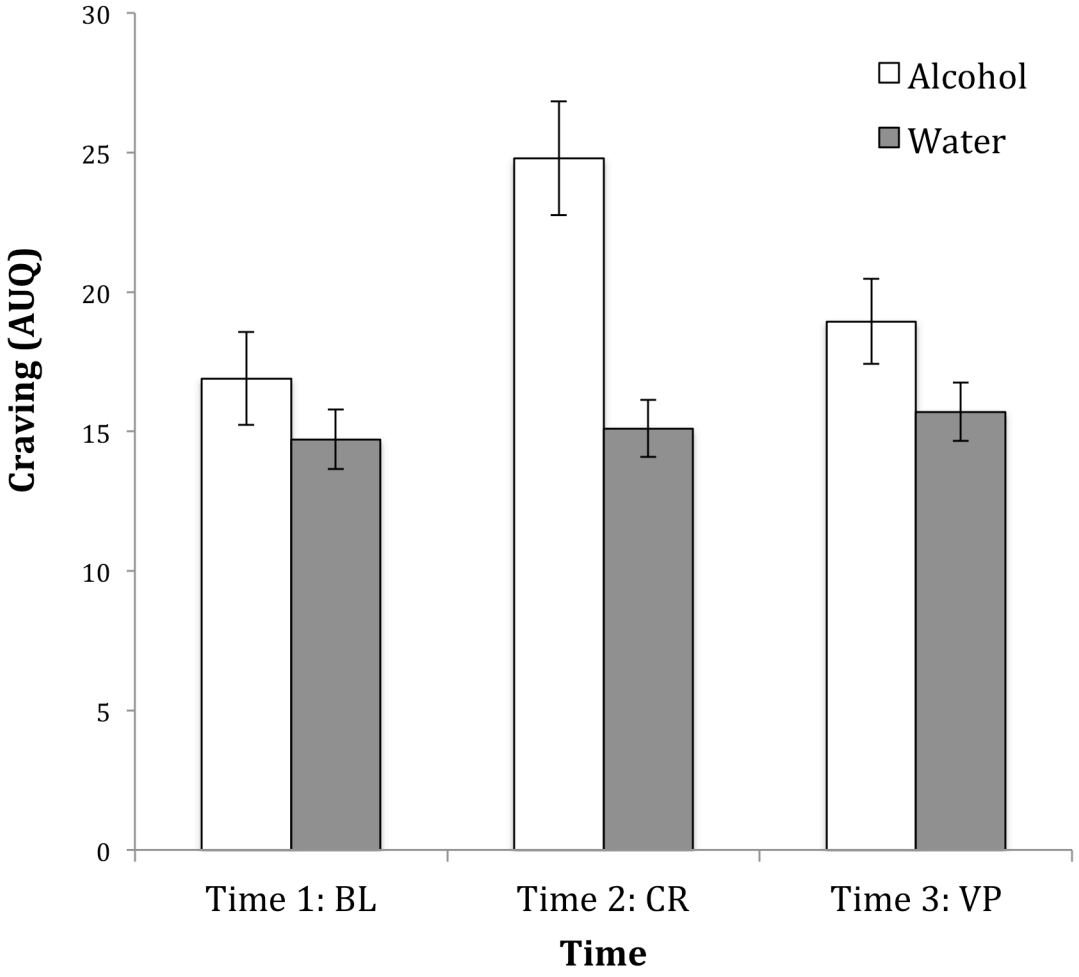

Figure 6. Cumulative AUQ scores at Time 1 (before cue reactivity), Time 2 (after cue reactivity and before visual probe task), and Time 3 (after visual probe task) separated by alcohol cue exposure sessions in white bars and water cue exposure sessions in gray bars. Values are sample means ± SEM.

17.30, $p < .001$). Bonferroni corrected ($\alpha = 0.0125$) post hoc t-tests revealed a significant increase in craving between baseline and cue reactivity within the alcohol cue reactivity session ($t(38) = 7.23$, $p < .001$, $d = 1.28$), with no change in craving between baseline and cue reactivity within the water cue reactivity session ($t(38) = 0.66$, $p = .513$, $d = 0.11$). There were no significant differences in craving reported at baseline between alcohol and water cue reactivity sessions ($p > 0.05$).

Planned t-tests were also run to examine the effects of the visual probe task on craving. During alcohol cue reactivity sessions, a significant decrease in craving was reported between completion of cue reactivity and the visual probe task ($t(38) = 4.96$, $p < .001$, $d = 0.97$). During water cue reactivity sessions, there was no difference in craving between completion of cue reactivity and the visual probe task ($t(38) = 1.29$, $p = .205$, $d = 0.18$).

Attentional bias. Figure 7 presents the means of individual median reaction times to probes that replace alcohol and neutral cues in both the alcohol and water cue reactivity sessions. A repeated measures ANOVA revealed a main effect of Trial ($F(1,38) = 15.50$, $p < .001$), subsumed under a Session x Trial interaction ($F(1,38) = 5.26$, $p = .027$). Bonferroni corrected ($\alpha = 0.025$) post hoc *t*-tests reveal a significant attentional bias towards alcohol cues with faster reaction times to probes that replaced alcohol cues during alcohol cue reactivity sessions ($t(38) = 4.39$, $p < .001$, $d = 0.72$). Participants did not show a significant attentional bias to probes that replaced alcohol cues during water cue reactivity sessions ($t(38) = 1.49$, $p = .146$, $d = 0.31$). Attentional bias to alcohol was significantly stronger during alcohol cue reactivity sessions than during water cue reactivity sessions ($t(38) = 2.29$, $p = .027$)**.**

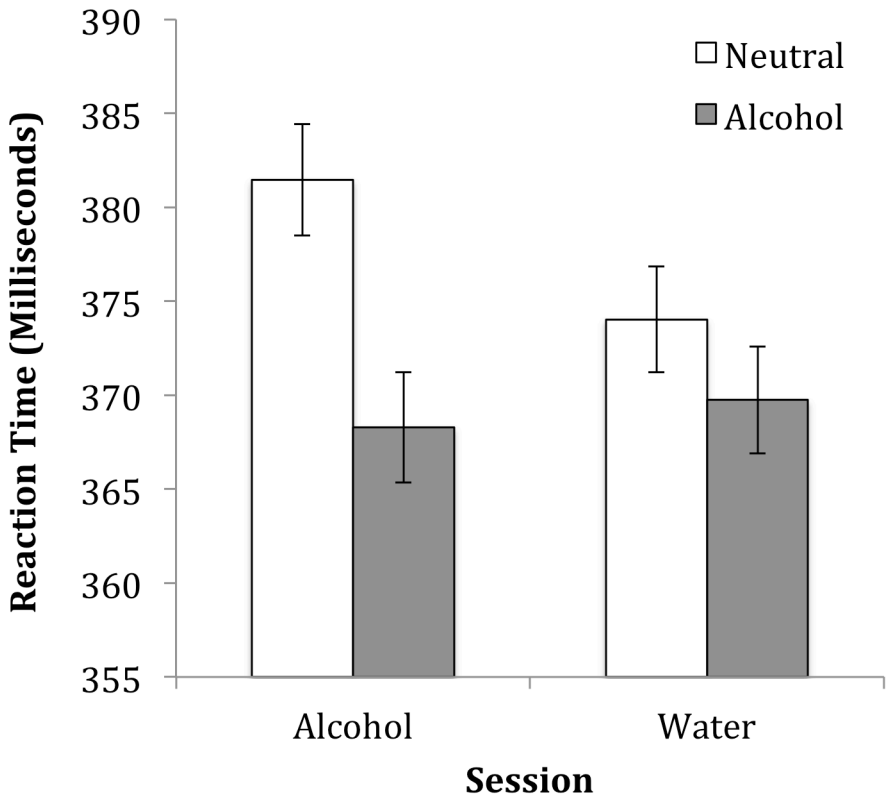

Figure 7. Attentional bias reaction times to probes that replace neutral cues in white bars and to probes that replace alcohol cues in gray bars separated by alcohol and water cue exposure sessions. Values are sample means of individual median reaction times ± SEM.

Craving and attentional bias. To examine the relationship between craving and attention, separate regression analyses were run to examine craving reported during cue reactivity as a predictor of attentional bias scores during the visual probe task. Craving reported after cue reactivity (immediately preceding visual probe task) did not significantly predict attentional bias to alcohol cues in either the alcohol session (r = .28, p = .081) or the water session (r = .02, p = .929). Lastly, craving difference scores between the alcohol and water session marginally predicted attentional bias change scores between sessions such that greater increases in craving from the water to the

alcohol session predicted greater increases in attentional bias from the water to the alcohol session (r = .31, p = .054) as shown in Figure 8.

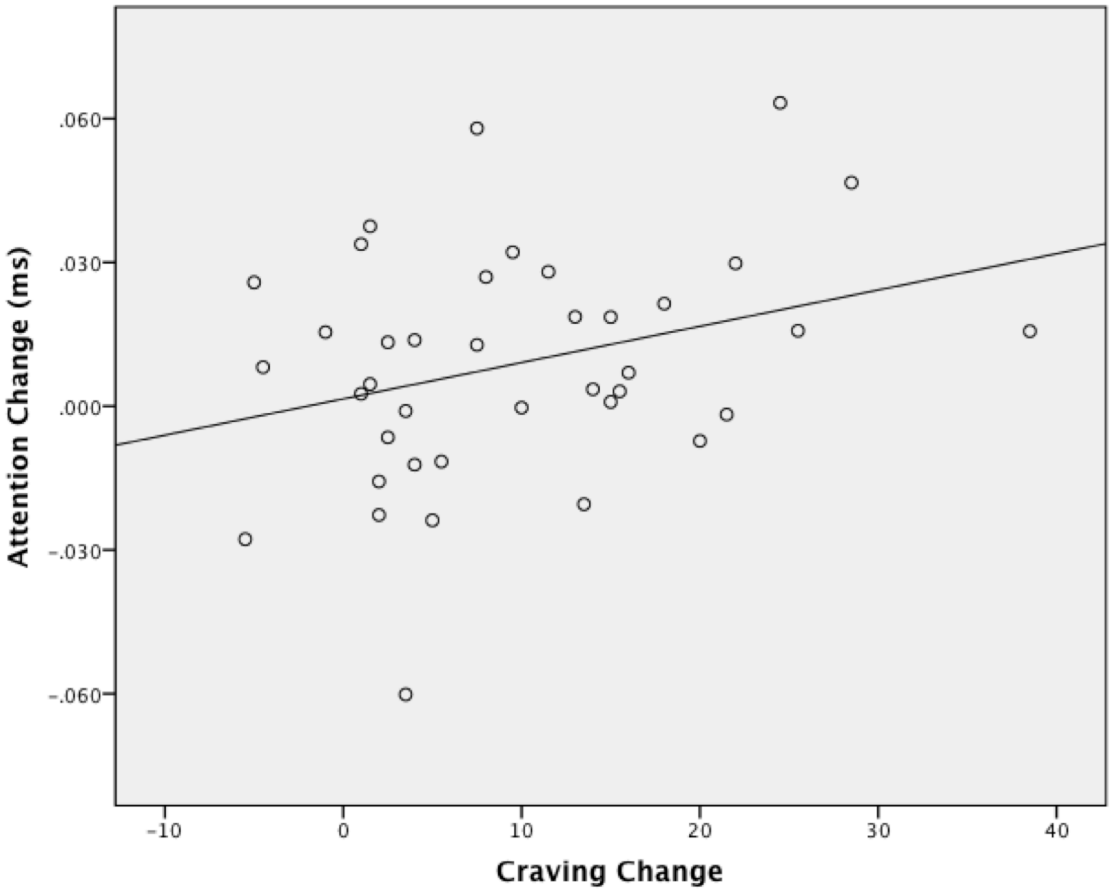

Figure 8. Observed between-session changes in attentional bias (milliseconds) by changes in craving (cumulative AUQ scores). Change scores were quantified by subtracting values obtained during water cue exposure sessions from values obtained during alcohol cue exposure sessions with positive scores indicating greater attentional biases and craving during alcohol sessions. The best fitting line is illustrated.

Discussion

Using a within-subjects *in vivo* alcohol cue reactivity paradigm, the effects of alcohol cue exposure on subjective craving and attentional bias to alcohol were examined within a population of underage drinkers. Three main results were obtained. First, exposure to *in vivo* alcohol cues increased subjective reports of craving. Second, following alcohol cue exposure, but not water cue exposure, attention was biased towards alcohol picture cues presented in a visual probe task. Third, craving did not predict attentional bias towards alcohol under control conditions in which craving reports were low but the relationship between craving and attention was strengthened following alcohol cue exposure. Within-subject differences in craving across session types marginally predicted within-subject differences in attentional bias with effect sizes consistent with previous literature (Field, Munafo, & Franken, 2009). These results are consistent with a core assertion of Franken's (2003) attentional bias model that drug craving should positively predict attentional bias to drug cues.

The present study found that underage drinkers reported robust increases in subjective craving following *in vivo* alcohol cue exposure. Within-session increases in craving, as measured by the AUQ, were observed following exposure to *in vivo* alcohol cues, with no changes in craving reported following exposure to water cues. Although the sample included both heavy and lighter drinkers, craving to alcohol cues overall was robust with an effect size (d = 1.28) larger than typically observed in adult populations (d = 0.53 Carter & Tiffany, 1999). Despite previous findings that cue reactivity responses distinguish heavy drinkers from light drinkers (Ihssen et al., 2011) and alcoholic from nonalcoholic adults and early adolescents (Monti et al, 1987; Tapert et al. 2003), cue-

elicited craving in the current study was not predicted by baseline rates of drinking or measures of alcohol-related problems. However, it should be noted that alcohol use disorder (AUD) status was not assessed and that 76.9% of the sample reported AUDIT scores below 16, which is considered as a threshold indicating a high level of alcohol problems (Babor et al., 2001). Future studies with greater proportions of problematic underage drinkers should formally assess AUD status to see if cue-elicited craving responses distinguish youth with AUDs from youth without AUDs.

The effects of alcohol cue exposure on attention were also in line with the experimental hypotheses. Exposure to *in vivo* alcohol cues strengthened attentional biases to pictorial alcohol cues subsequently presented in a visual probe task. These results extend previous findings in which attentional biases towards alcohol are strengthened following exposure to alcohol picture cues (Cox, Yeates, & Regan, 1999) by using the visual probe task as a novel procedure to assess attentional bias. In the current study, participants only exhibited an attentional bias to alcohol cues following *in vivo* alcohol cue exposure (Cohen's $d = .72$). During water cue reactivity sessions, participants did not exhibit significant attentional biases to probes that replaced alcohol cues in the visual probe task (Cohen's $d = .31$). The greater bias towards alcohol cues during the alcohol session does not appear to be the result of faster reaction times to probes that replaced alcohol cues, but rather a result of slower reaction times to probes that replaced neutral cues. Across session types, reaction times to probes that replaced alcohol cues were nearly identical. Instead, slower reaction times to probes that replaced neutral cues were observed during alcohol cue exposure sessions compared to the water cue exposure sessions. Therefore, I interpret the results as supporting the hypothesis that

exposure to *in vivo* alcohol cues results in delayed disengagement of attention from subsequent alcohol cues when probes replaced neutral cues. This is to be distinguished from the possibility of enhanced attentional orienting response resulting in quicker reaction times to probes that replace alcohol cues, which was not the case in the current study. This disengagement mechanism is consistent with other interpretations of attentional bias during visual probe tasks when cues are presented for 500ms or longer in which the stimulus duration is long enough for participants to shift attention from one stimulus to the other (Field, Schoenmakers, & Wiers, 2008).

The measurement of both craving and attentional bias allowed for examination of a positive relationship between these two constructs as predicted by the attentional bias model (Franken, 2003). First, separate regression analyses were run to assess craving as a predictor of attentional bias in each of the alcohol cue and water cue sessions. There was no relationship between craving and attentional bias following water cue exposure (r = .02). However, Franken's model (2003) predicts that increases in craving should lead to increased attentional biases, thus we would expect the relationship between craving and attentional bias to be stronger when craving is relatively high. Indeed, there was a stronger predictive relationship when craving was relatively high during the alcohol cue exposure session (r = .28). These findings are in line with a meta-analysis of studies measuring both craving and attention (Field, Munafo, & Franken, 2009), in which the relationship between these two constructs was stronger among studies in which craving was manipulated (r = .23 in high craving conditions, r = .08 in low craving conditions). Another regression analysis tested the possibility that craving mediates the relationship between cue exposure and attention by using the within-subject differences in craving

across session type to predict within-subject differences in attentional bias (Judd, Kenny, & McClelland, 2001). Craving change scores between sessions marginally predicted attentional bias scores between sessions ($r = .31$, $p = .054$) lending support to a positive relationship between these two constructs.

Field, Munafo, and Franken (2009) identified several factors that moderate the relationship between craving and attention, at least two of which may apply to the modest effect sizes found in the current study. First, the magnitude of positive correlations between craving and attention is weaker in alcohol studies compared to studies with other drugs of abuse, although explanations for this finding are unclear. Second, weaker associations are found between craving and attention among studies utilizing indirect measures of attention such as reaction times from the visual probe task used in the current study. Measures that infer attentional bias on the basis of reaction times may not provide a measure sensitive enough to fully capture the relationship between craving and attention. For these reasons, even though the overall effect sizes were comparable and actually greater than the modest but significant positive correlations found in the meta-analysis of studies measuring both of these constructs (Field, Munafo, & Franken, 2009), our study may have lacked sufficient power to detect a statistically significant association between the two constructs. Future studies are recommended to use direct measures of selective attention such as eye movement monitoring.

A further challenge to assessing the relationship between craving and attentional bias may arise from the presence of within-session changes in the level of craving. During alcohol cue reactivity sessions in which levels of subjective craving were elevated prior to beginning the visual probe task, significantly lower levels of craving were

reported after completion of the task. This decrease in craving was observed despite the finding that participants expressed an attentional bias to alcohol cues throughout the visual probe tasks in alcohol cue reactivity sessions. Similarly, other studies with longer durations of cue reactivity have also reported within-session decreases in craving for alcohol (Kamboj et al., 2011; Monti et al., 1993). One interpretation for decreases in craving is that repeated nonreinforced presentations of alcohol pictures during the visual probe result in the extinction of the craving response as predicted by classical learning theory. Although it is possible that craving responses extinguished throughout the visual probe task in the current study, we do not know if craving was higher or lower than expected if alcohol cues had not been presented. Therefore without a proper control group, we do not know the typical rate of decay for craving over this period of time. Regardless of the specific mechanism, rapid fluctuations in craving may contribute to the difficulty in measuring the relationship between craving and attention.

Ultimately, the relationship between alcohol craving and attention warrants further research. Despite the consistency in effect sizes between the current study and previous analyses, much of the variance in attentional bias remains unexplained proving somewhat problematic for theories positing a direct relationship between the two. It remains possible that alcohol cues may be automatically detected and can influence alcohol-seeking behavior in the absence of conscious processes like subjective craving. As outlined by Tiffany's cognitive processing model of drug use (1990), drug-seeking and consummatory behaviors become automatic after periods of extended use. In this model, craving is not an automatic but rather a controlled process that may be elicited as a result of disruptions to the automatic pattern of drug use. If attentional biases reflect

automatic processing, then a bias in attention towards alcohol and experienced subjective craving need not occur in tandem. Such distinctions are critical to clinical treatments aimed at reducing either craving (Glautier & Drummond, 1994; Monti & Rohsenow, 1999) or attentional biases to alcohol (Fadardi & Cox, 2009; Schoenmakers et al., 2010). If the two are distinct phenomena and both act to motivate drug use, treatments may benefit most by reducing both craving and attentional bias, and not one or the other.

One final noteworthy finding is that attentional biases to alcohol cues after water exposure negatively correlated with alcohol problems as measured by the AUDIT suggesting that those with more alcohol problems had weaker biases to alcohol cues under control conditions. This finding has some similarities to previous literature, in which heavy drinkers have shown attentional biases to cue presentations of longer than 500ms (Field et al., 2004; Townshend & Duka, 2001) whereas abstinent, treatment-seeking alcohol dependent individuals sometimes show an avoidance of such cues (Stormark et al., 1997; Townshend & Duka, 2007) which may reflect strategies implemented to avoid processing of alcohol-related cues. Given that the current sample represents underage drinkers in college, it is possible that drinkers with more alcohol-related problems have developed alcohol avoidance strategies in order to maintain a high level of academic functioning. Although high scores on the AUDIT may reflect a degree of alcohol problems that contribute to the avoidance of cues observed in other populations of drinkers, it is important to note that none of the participants were treatment-seeking nor abstinent, and motivational factors were not otherwise assessed. Further studies are needed to clarify the relationship between alcohol-related problems and attentional bias to alcohol cues among non-treatment seeking drinkers.

In summary, the current study showed that underage drinkers express greater subjective craving following exposure to *in vivo* alcohol cues, and that attention becomes biased to subsequent alcohol cues. Furthermore, the effect of cue exposure on increasing attentional bias appears to be the result of a disengagement mechanism as suggested by slower reaction times during alcohol cue sessions to probes that replace neutral cues. Although cue exposure initially elevated craving and biased attention towards alcohol, the strength of craving decreased within the course of the session. However, further work is needed to determine if these observed decreases are the result of extinction learning, or if they reflect the typical rate of decay of craving over time. In addition to the overall increases in craving and attentional bias following alcohol cue exposure, the strength of the relationship between the two constructs was consistent with past research indicating a small, but potentially meaningful positive relationship.

CHAPTER 5

EXPERIMENT 3: EXTENDED ALCOHOL CUE EXPOSURE EFFECTS ON CRAVING AND ATTENTIONAL BIAS

Experiment 2 provided support for Franken's attentional bias model (2003) in that exposure to alcohol cues increased subjective craving and biased attention to alcohol cues. Further, there was a marginally significant positive relationship between craving and attention such that increases in subjective craving following alcohol cue exposure were associated with increases in attentional bias to alcohol. Experiment 3 aimed to further explore alcohol cue exposure effects on craving and attentional bias, while also examining the relationship between these two constructs. To date, no research has examined if momentary decreases in craving lead to decreases in attentional bias to alcohol, which was the primary aim of Experiment 3.

This potential relationship between craving and attentional bias has significant implications for interventions that aim to reduce either of these constructs. Treatments that aim to reduce craving include cue exposure therapies, and there is also recent evidence that medications like naltrexone reduce both craving and drinking outcomes (Miranda et al., 2013). Also, attentional retraining therapies have been extended into the realm of substance use intervention (e.g., Attentional Bias Modification Training, ABM; Alcohol Attention-Control Training Program, AACTP). These treatments utilize experimental paradigms typically used to assess attentional bias, and modify them in order to train biases away from alcohol. To date, results show that such treatments are effective at decreasing attentional bias towards alcohol cues (Schoenmakers et al., 2010) and that harmful drinkers exhibit post-training reductions in alcohol consumption with

improvements still evident at a 3-month follow-up (Fadardi & Cox, 2009). Given that some treatments aim to reduce either craving or attentional bias to alcohol, whether or not these two constructs are positively associated is of critical importance. For example, if a treatment successfully reduces craving but not attentional biases to alcohol, then an individual would be at risk of relapse to the extent that attentional biases to alcohol motivate alcohol consumption in the absence of craving. However, if reductions in craving also lead to reductions in attentional bias, then treatments that successfully reduce craving should presumably reduce attentional bias to alcohol as well.

Experiment 3 employed a between-groups design to assess the effects of extended alcohol cue exposure on craving and attention. When cue exposure procedures are carried out over an extended period of time, participants have been shown to report initial rises in craving followed by decreases in craving over time (Kamboj et al., 2011) with one study in particular demonstrating peak craving after 6 minutes of alcohol cue exposure followed by gradual but significant decreases in craving (Monti et al., 1993). The experimental hypothesis consistent with Franken's attentional bias model (2003) is that participants receiving extended alcohol cue exposure will report decreases from peak reports of craving, and as a result will express weaker attentional biases to alcohol cues compared to participants receiving a shorter alcohol cue exposure period. Furthermore, within-session changes in craving were hypothesized to predict within-session changes in attentional bias to alcohol.

Method

Participants

Eighty undergraduate students were invited to participate in the study as an opportunity to fulfill course requirements or to receive financial compensation. Students, 18 to 20 years of age, were eligible to participate if they drank at least one beer on a weekly basis over the past month. Individuals were considered ineligible if currently seeking treatment for alcohol problems or if having received treatment in the past 30 days.

Table 9. Experimental Design.

		Cue Reactivity (CR) Protocol							
	Time 1 Baseline		Block 1	Block 2	Block 3	Block 4	Block 5	Block 6	Time 2 Post CR
Group Short	VP	Rest	W	W	W	W	A	A	VP
Group Long	VP	Rest	A	A	A	A	A	A	VP

Notes: VP = Visual Probe Task, W = Water Cues, A = Alcohol Cues, Subjective measures of craving completed at Time 1, after each 3-min block of the cue reactivity protocol, and at Time 2.

Procedures

General Procedure. The basic study design is outlined in Table 9. Participants were randomly assigned to one of two groups that differed on the basis of alcohol cue exposure duration in the cue reactivity procedure. All participants first provided demographic information. Next, participants completed a baseline visual probe task (Time 1) followed by the cue reactivity procedure and then completed a final visual probe task (Time 2) to assess changes in attentional bias towards alcohol. For the cue reactivity procedure, 'Group Long' received an extended alcohol cue exposure period, whereas 'Group Short' received a brief alcohol cue exposure period. Both groups received the

same visual probe tasks, which included the same stimuli. Additional individual difference measures were collected after the final visual probe task due to the concern that the nature of these assessments (e.g., recalling drinking episodes) might affect craving and attentional bias to alcohol. All participants signed informed consent before beginning the study. The Brown University institutional review board approved this study.

Cue Reactivity (CR). Participants were asked to abstain from drinking the morning of the study and prior to starting, participants were breath-tested to ensure a Blood Alcohol Content (BAC) of 0.00 (all participants had a BAC of 0.00). Participants then received standardized instructions about the cue reactivity assessments while becoming acclimated to the laboratory. Prior to cue exposure, participants indicated which one of three beer options they most commonly drink and whether they were more likely to drink that beer from a cup or glass. The three beer options represented the spectrum of beer choices popular among college student drinkers and covered the beer preferences of the study participants.

Sessions began with a 3-minute relaxation period, in which participants sat quietly and did nothing. Next participants were given six consecutive 3-minute blocks of beverage exposure. For Group Long, each block was identical as participants were instructed to hold and smell a cup or glass of beer for 3 minutes, with the type of beer and container matching that which the participant indicated as having the most experience with outside of the lab. For Group Short, participants were instructed to hold and smell a glass of water for 3 minutes to control for exposure to a potable liquid for the first four blocks. For the last two blocks, participants in Group Short were exposed to beer in the

same manner as participants in Group Long. All participants in all blocks of beverage exposure were asked to smell the beverage for 5 seconds each time a tone sounded with 13 tones delivered during each 3-minute block of time with variable intervals to ensure that all received the same olfactory exposure. Following each 3-minute block, participants completed measures of subjective craving. Subjective craving measured prior to the beverage exposure blocks represents the baseline measure of craving (Time 1), while subjective craving reported after the sixth and final block represents the final craving report (Time 2). Compliance was monitored by observation through a one-way mirror and all participants complied with the study protocol.

Visual Probe. All participants completed visual probe tasks to assess attentional bias to alcohol cues at baseline immediately before the CR procedure (Time l) and immediately after the CR procedure (Time 2). There was no difference in the visual probe task procedure at these different timepoints. Participants were seated in front of a laptop computer and instructed to identify the location of a single probe stimulus, which always followed the presentation of a pair of pictorial stimuli. The task began with six practice trials, in which neutral picture pairs were presented. Following a short break, two buffer trials were presented with neutral pairs again, followed by 80 critical trials, in which alcohol-control picture pairs were presented. Each trial began with a fixation cross presented in the center of the screen for 500 ms, immediately followed by the bilateral presentation of a picture pair for 1000 ms, with pictures positioned to the left and right of the previously presented fixation cross. After picture offset, a visual probe stimulus was presented on either the left or right side of the screen where the picture stimulus was presented. The visual probe stimulus was an "X" presented in red font, and the

presentation of the probe stimulus required the participant to press one of two response keys ("A" for left and "L" for right) on the keyboard indicating on which side the probe appeared. After making a response, there was an intertrial interval of 500 ms before the next fixation cross appeared. Throughout the 80 critical trials, each alcohol-control picture pair was presented eight times, with the alcohol-related picture being presented four times on the left and four times on the right of the screen. Probes replaced alcohol-related and control pictures with equal frequency, and appeared on each side of the screen with equal frequency. Attentional bias was indicated by shorter (i.e., faster) reaction times to probes replacing alcohol-related pictures than to those replacing control pictures. Following completion of the visual probe task, participants rated their urge to drink to assess post-task levels of craving.

Measures

Alcohol Craving. Participants completed the Alcohol Urge Questionnaire (AUQ; Bohn, Krahn & Staehler, 1995), an 8-item measure of momentary craving with items rated on a scale from 1 to 7, with total scores on the questionnaire ranging from 8 to 56 and higher scores representing greater momentary craving.

Alcohol Use. Baseline (pre-study) drinking levels were assessed using the 90-day timeline follow-back interview (TLFB; Sobell & Sobell 1992). The TLFB was scored for the percentage of drinking days and heavy drinking days (>5 standard drinks for males, >4 standard drinks for females) in the last 90 days, and the number of standardized drinks per drinking day. Two separate measures assessed alcohol use and alcohol-related problems. First, participants completed the Rutgers Alcohol Problem Index (RAPI; White & Labouvie, 1989); a 23-item measure for assessing adolescent problem drinking

and negative consequences that result from drinking including problems at school/work, interpersonal difficulties, emotional troubles, and signs of tolerance. Items were rated on a scale of '0 = never' to '4 = more than 10 times,' indicating the number of occurrences of alcohol-related problems in the past three months. Norms have been established on adolescent communities and treatment samples (12 to 21 years old), which allows for comparisons of problem drinking score on an individualized basis. Second, the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001) was administered to gauge hazardous and harmful patterns of alcohol use. The AUDIT consists of 10 short questions based on three domains; hazardous alcohol use, dependence symptoms, and harmful alcohol use. The items were also rated on likert-type 0-4 scales with a total possible score of 40, although scores above 8 indicate hazardous patterns of drinking. A subset of participants (n = 38) also responded to an alcohol use history question indicating the number of years since first consuming alcohol.

Data Analysis

Descriptives and Bivariate Correlations. Group and subgroup comparisons on demographic and other individual differences measures were conducted using independent samples *t*-tests for continuous variables and chi-square tests for categorical variables. To explore the relationships between individual difference measures of drinking and baseline rates of craving and attentional bias (before between-group manipulations), these measures were investigated using bivariate correlations.

Craving for alcohol. The AUQ was administered at seven time points: at baseline before the first visual probe task (Time 1), and after each of the six CR exposure blocks with Time 2 representing the final craving report after the sixth block. Summary

AUQ scores were used as the measure of craving in all analyses. To examine group differences in craving at the critical timepoints, total AUQ scores were analyzed using a mixed-design 2 x 2 analysis of variance (ANOVA), with Group (2, Group Short, Group Long) as the between-subjects factor, and Time [2, Time 1 (Baseline), Time 2 (post CR Block 6)] as the within-subjects factor. Craving was also compared in a series of Bonferroni corrected t-tests ($\alpha = 0.0125$) to assess group differences in craving at Time 1 and Time 2. A chi-squares analysis was run to compare group differences in the proportion of individuals who reported peak craving at Time 2. Peak craving was defined as each individual's highest AUQ score reported throughout the CR procedure. Craving was also compared between two subgroups of different craving responders in Group Long, those who reported peak craving at the end of the CR procedure (Subgroup Peak, $n = 17$), and those who did not report peak craving at the end of the CR procedure (Subgroup Decrease, $n = 23$).

Attentional bias. For the visual probe task, trials with errors (incorrect identification of probe side) were removed (1.2%) and median reaction times were determined for each participant's responses to probes that replaced alcohol cues and probes that replaced neutral cues. Median scores were used due to positive skewness among the reaction times. Attentional bias scores were calculated for each participant by subtracting the median reaction time to probes that replaced alcohol cues from the median reaction time to probes that replaced neutral cues. Attentional bias scores greater than zero indicate an attentional bias to alcohol cues. To examine group differences, attentional bias scores were analyzed using a mixed-design 2 x 2 analysis of variance (ANOVA), with Group (2, Group Short Exposure, Group Long Exposure) as the

between-subjects factor, and Time [2, Time 1 (Baseline), Time 2 (post CR)] as the within-subjects factor. Separate Bonferroni corrected *t*-tests ($\alpha = 0.025$) were run to compare group differences in attentional bias scores at Time 1 and Time 2.

Attentional biases were also analyzed for the subgroups in Group Long using a separate mixed-design 2 x 2 ANOVA with Subgroup (2, Subgroup Peak, Subgroup Decrease) as the between-subjects factor, and time [2, Time 1 (Baseline), Time 2 (post CR)] as the within-subjects factor. Separate Bonferroni corrected *t*-tests ($\alpha = 0.025$) were run to compare group differences in attentional bias scores at Time 1 and Time 2.

Craving and attentional bias. A series of regression analyses were run to examine the relationship between craving and attention. Specifically, for each group within-subject changes in craving scores from Time 1 to Time 2 were used to predict within-subject changes in attentional biases from Time 1 to Time 2 as recommended to test for within-subjects mediation (Judd, Kenny, & McClelland, 2001).

Table 10
Baseline Participant Characteristics by Group: Percentage or Mean (With Standard Deviation in Parentheses)

Variable	Group Short (n = 40)	Group Long (n = 40)	Overall (N = 80)
Age	19.2 (0.7)	19.2 (0.9)	19.1 (0.8)
Gender (Female)	57.5	57.5	57.5
Race[a]			
Caucasian	57.5	57.5	57.5
African-American	12.5	7.5	10.0
Hispanic	5.0	7.5	6.3
Asian	25.0	27.5	26.3
RAPI	5.7 (3.3)	6.4 (5.6)	6.1 (4.5)
AUDIT	10.0 (4.8)	9.4 (4.3)	9.7 (4.6)
Percent Drinking Days[b]	23.7 (11.4)	22.9 (9.7)	23.3 (10.5)
Percent Heavy Drinking Days[b]	9.7 (9.0)	10.1 (9.3)	9.9 (9.1)
Drinks Per Drinking Day[b]	3.8 (1.8)	3.6 (1.6)	3.7 (1.7)

Note. [a] Races were not considered mutually exclusive [b] Derived from the 90-day Timeline Follow-Back interview conducted at baseline; AUDIT = Alcohol Use Disorders Identification Test; RAPI = Rutgers Alcohol Problem Index

Results

Descriptives and bivariate correlations. Table 10 shows descriptive information for the sample separated by group. There were no group differences in any demographic or individual difference measures of alcohol-related problems and measures of baseline drinking (all p's > .10). The subgroups of craving responders in Group Long also did not differ with regards to any demographic or individual difference measures of alcohol-related problems and measures of baseline drinking (all p's > .10) as shown in Table 11.

Table 11
Baseline Participant Characteristics by Subgroups of Group Long: Percentage or Mean (With Standard Deviation in Parentheses)

Variable	Subgroup Decrease (n = 23)	Subgroup Peak (n = 17)	Group Long Overall (N = 40)
Age	19.3 (0.9)	19.1 (0.9)	19.2 (0.9)
Gender (Female)	47.8 (n = 11)	70.6 (n = 12)	57.5
RAPI	6.2 (4.8)	6.6 (6.6)	6.4 (5.6)
AUDIT	9.2 (4.1)	9.7 (4.7)	9.4 (4.3)
Percent Drinking Days[a]	23.8 (10.5)	21.6 (8.6)	22.9 (9.7)
Percent Heavy Drinking Days[a]	9.7 (9.0)	10.1 (9.3)	10.1 (9.3)
Drinks Per Drinking Day[a]	3.8 (1.6)	3.5 (1.6)	3.6 (1.6)

Note. [a] Derived from the 90-day Timeline Follow-Back interview conducted at baseline; AUDIT = Alcohol Use Disorders Identification Test; RAPI = Rutgers Alcohol Problem Index

Bivariate correlations among individual predictor variables and the main outcome variables at baseline are presented in Table 12. Significant correlations were present between all measures of alcohol problems and measures of baseline alcohol use (all p's < .01). Craving at baseline was significantly positively correlated with scores reported on the RAPI (r = .36, p = .001) and AUDIT (r = .42, p <. 001), percent of drinking days in the past ninety days (r = .23, p = .03), standard drinks consumed per drinking day (r = .28, p = .011), and the number of years since first consuming alcohol (r = .43, p = .008). The percent of drinking days in the past ninety days also significantly correlated with the number of years since first consuming alcohol (r = .40, p = .012). Attentional bias towards alcohol cues during the baseline visual probe task was not significantly

correlated with craving at baseline or any measure of alcohol-related problems or baseline alcohol use (all *p*'s > .05).

Table 12
Correlation Matrix for Baseline Outcome and Predictor Variables

Measure	1	2	3	4	5	6	7
1. Craving (Baseline)	___						
2. Attentional Bias (Baseline)	.09	___					
3. RAPI	.36**	.05	___				
4. AUDIT	.42**	.08	.63**	___			
5. Drinking Days (%)[a]	.24*	.21	.38**	.52**	___		
6. Drinks Per Drinking Day[a]	.28*	.02	.46**	.62**	.33**	___	
7. Years Since First Use[b]	.43**	.01	.17	.25	.40*	.28	___

Note. Craving reflects subjective ratings scored at Time 1 (Baseline) prior to cue exposure. Attentional bias reflects the bias of median reaction times during visual probe task at Time 1 (Baseline) prior to cue exposure; RAPI = Rutgers Alcohol Problem Index (higher scores indicate greater severity of alcohol-related problems); AUDIT = Alcohol Use Disorders Identification Test (higher scores indicate greater severity of alcohol-related problems); [a]derived from the 90-day Timeline Follow-Back interview conducted during first session; [b]collected only from subsample (n = 38); *$p < .05$, **$p < .01$.

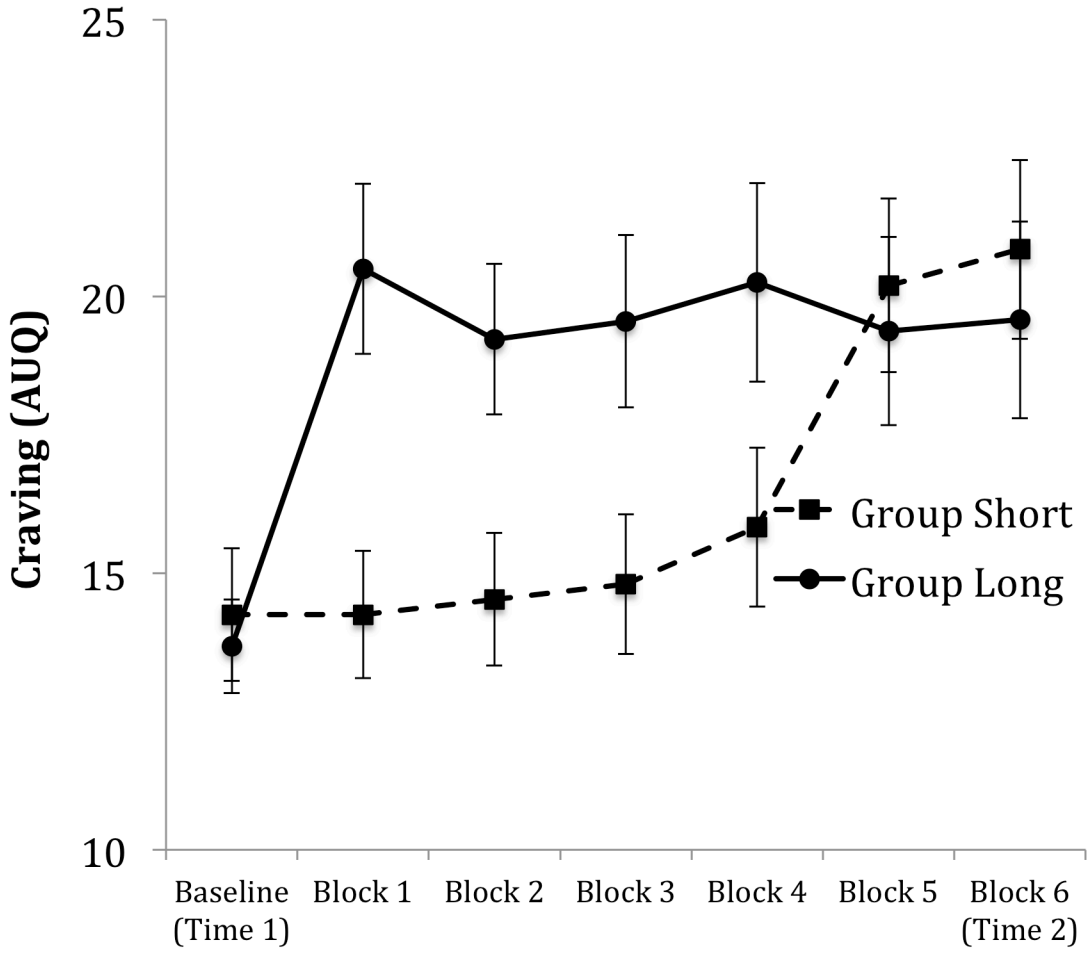

Figure 9. Cumulative AUQ scores at Time 1 (Baseline), after each block of the cue reactivity protocol including Time 2 (after Block 6), separated by Group Short with dotted lines and square markers and Group Long in solid lines and circle markers. Group Short received water cue exposure for Blocks 1-4, whereas Group Long received alcohol cue exposure for Blocks 1-4. Both groups received alcohol cue exposure for Blocks 5-6. Values are sample means ± SEM.

Craving for alcohol. Figure 9 presents each group's mean levels of subjective craving (AUQ scores) measured at Time 1 and after each of the six 3-min blocks of cue exposure. Total AUQ scores were analyzed using a mixed-design 2 x 2 analysis of variance (ANOVA), with Group (2, Group Short Exposure, Group Long Exposure) as the between-subjects factor, and Time [2, Time 1 (Baseline), Time 2 (post CR Block 6)] as the within-subjects factor. There was a main effect of time [$F(1,78) = 36.43$, $p < .001$]

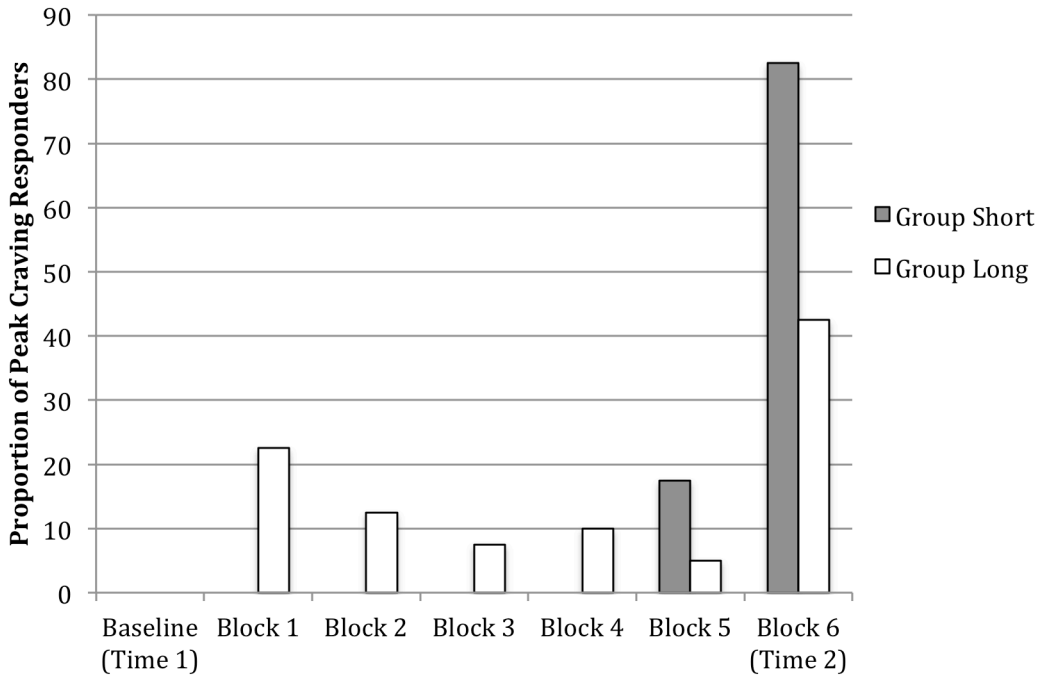

Figure 10. Proportions of peak craving responders at Time 1 (Baseline), and after each block of the cue reactivity protocol including Time 2 (after Block 6), separated by Group Short with dark gray bars and Group Long with white bars. Peak craving was defined as the highest reported AUQ score for each individual.

such that participants reported greater craving at Time 2 than at Time 1. The hypothesized Time x Group interaction was not significant [$F(1,78) = .03$, $p = .87$]. Independent group *t* tests indicated that the experimental groups did not report significantly different craving at Time 1 [$t(78)=1.07$, $p = .29$] or Time 2 [$t(78)=.53$, $p =.60$]. However a significantly greater proportion of individuals in Group Short reported peak craving at the end of the CR procedure than those in Group Long ($\chi^2 = 13.65$, $p < .001$) as seen in Block 6 of Figure 10.

Inspection of peak craving responders revealed two subgroups of comparable size for Group Long: those who reported peak craving after Block 6 (Subgroup Peak; n = 17), and those who did not report peak craving after Block 6 (Subgroup Decrease; n = 23). Figure 11 presents each subgroup's mean levels of subjective craving (AUQ scores) measured at Time 1 and after each of the six 3-min blocks of cue exposure. These subgroups did not differ significantly with regards to craving reported at Time 1 [$t(38)=.21$, $p=.84$], however Subgroup Peak reported significantly greater craving than Subgroup Decrease at Time 2 [$t(38)=2.59$, $p=.013$].

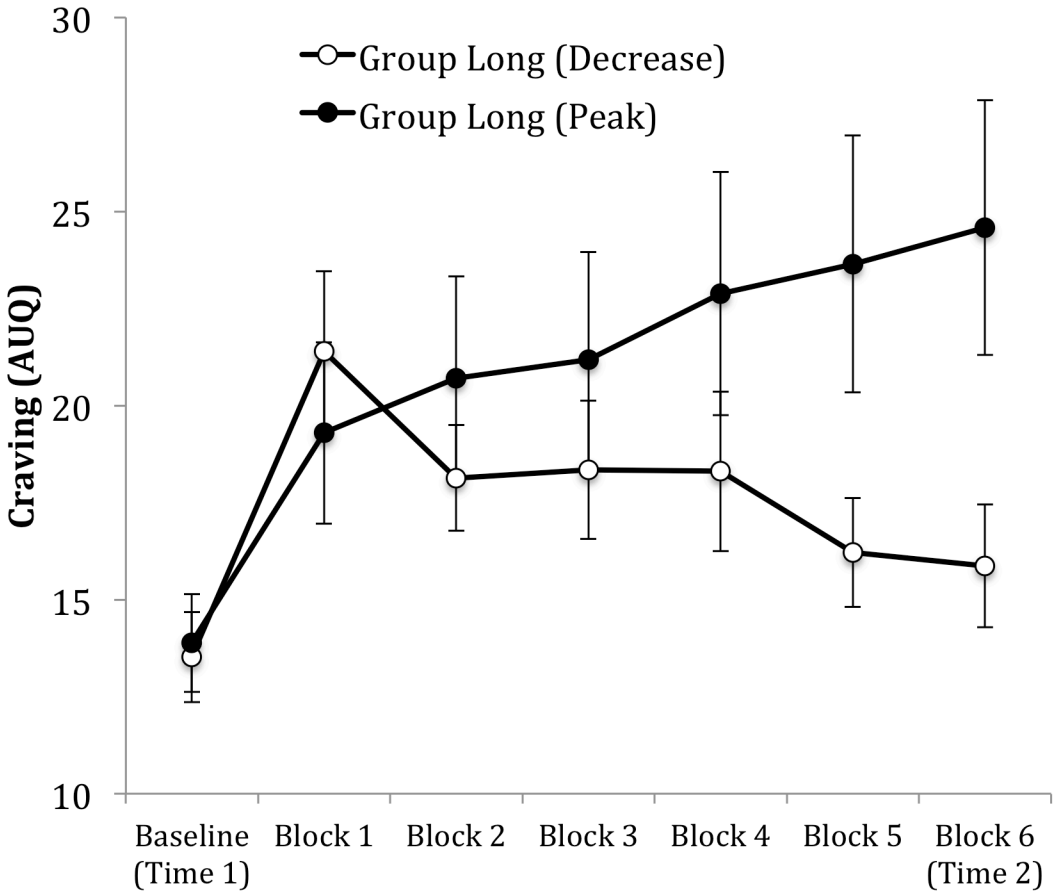

Figure 11. Cumulative AUQ scores at Time 1 (Baseline), after each block of the cue reactivity protocol including Time 2 (after Block 6), separated by Group Long (Decrease) with solid lines and open circle markers and Group Long (Peak) with solid lines and closed circle markers. Values are sample means ± SEM.

Attentional bias. Attentional bias scores were analyzed using a mixed-design 2 x 2 analysis of variance (ANOVA), with experimental group (2, Group Short Exposure, Group Long Exposure) as the between-subjects factor, and time [2, Time 1 (Baseline), Time 2 (post CR)] as the within-subjects factor. There was a main effect of time [$F(1,78) = 5.10$, $p = .027$] such that participants expressed greater attentional biases to alcohol cues following the CR procedure. The hypothesized Time x Group interaction was not significant [$F(1,78) = .44$, $p = .51$]. Independent group *t* tests indicated that the experimental groups did not have significantly different attentional bias scores at Time 1 [$t(78)=1.06$, $p = .29$] or Time 2 [$t(78)=.26$, $p =.80$]. Within-subject *t* tests were also performed for each group to examine if attention was significantly biased towards alcohol at either of Time 1 or Time 2. Group Short did not exhibit significant attentional biases towards alcohol at Time 1 [$t(39)=0.37$, $p = .71$], but did exhibit significant attentional biases towards alcohol at Time 2 [$t(39)= 3.25$, $p = .002$]. Similarly, Group Long also did not exhibit significant attentional biases towards alcohol at Time 1 [$t(39)= 1.76$, $p = .09$], but exhibited significant attentional biases towards alcohol at Time 2 [$t(39)= 3.11$, $p = .003$].

Attentional biases were also analyzed for the subgroups in Group Long using a separate mixed-design 2 x 2 ANOVA with Subgroup (2, Subgroup Peak, Subgroup Decrease) as the between-subjects factor, and time [2, Time 1 (Baseline), Time 2 (post CR)] as the within-subjects factor. There was a significant Time x Subgroup interaction [$F(1,38)=7.89$, $p = .008$]. Independent group *t* tests show that these subgroups did not have significantly different attentional bias scores at Time 1 [$t(38)=0.94$, $p = .35$] but that Subgroup Peak had significantly greater attentional biases to alcohol cues at Time 2

[$t(38)=2.21$, $p=.033$]. Figure 12 presents the mean attentional bias scores at Time 1 and Time 2 for each subgroup as well as Group Short for comparison.

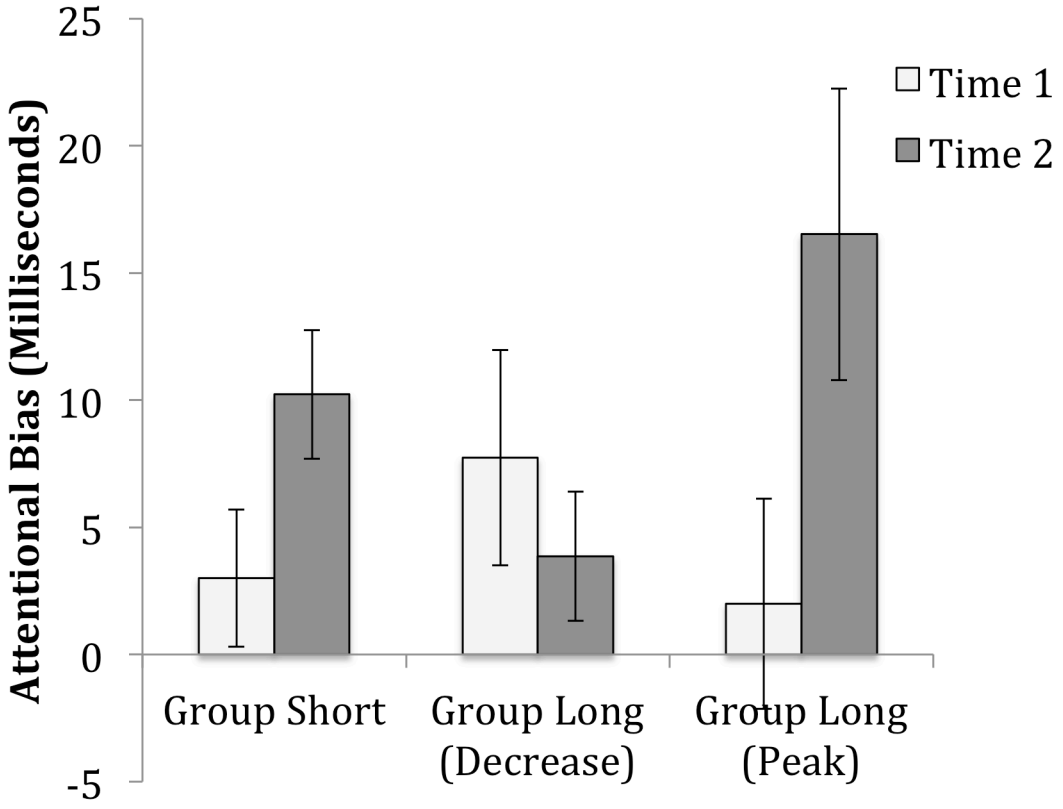

Figure 12. Attentional bias scores at Time 1 (Baseline) in light gray bars and at Time 2 (after CR procedure) in dark gray bars, shown separately for Group Short (n = 40), Group Long (Decrease, n = 23), and Group Long (Peak, n = 17). Values are sample means of attentional bias scores ± SEM.

Craving and attentional bias. To examine the relationship between craving and attention, separate regression analyses were run for each group to examine if changes in craving predicted changes in attentional bias scores from Time 1 to Time 2. For Group Short, craving difference scores did not significantly predict attentional bias change scores between Time 1 and Time 2 ($r = .24$, $r^2 = .06$, $p = .14$). For Group Long, craving

differences scores significantly predicted attentional bias change scores, such that greater increases in craving from Time 1 to Time 2 predicted greater increases in attentional bias from Time 1 to Time 2 ($r = .57$, $r^2 = .33$, $p < .001$) as shown in Figure 13.

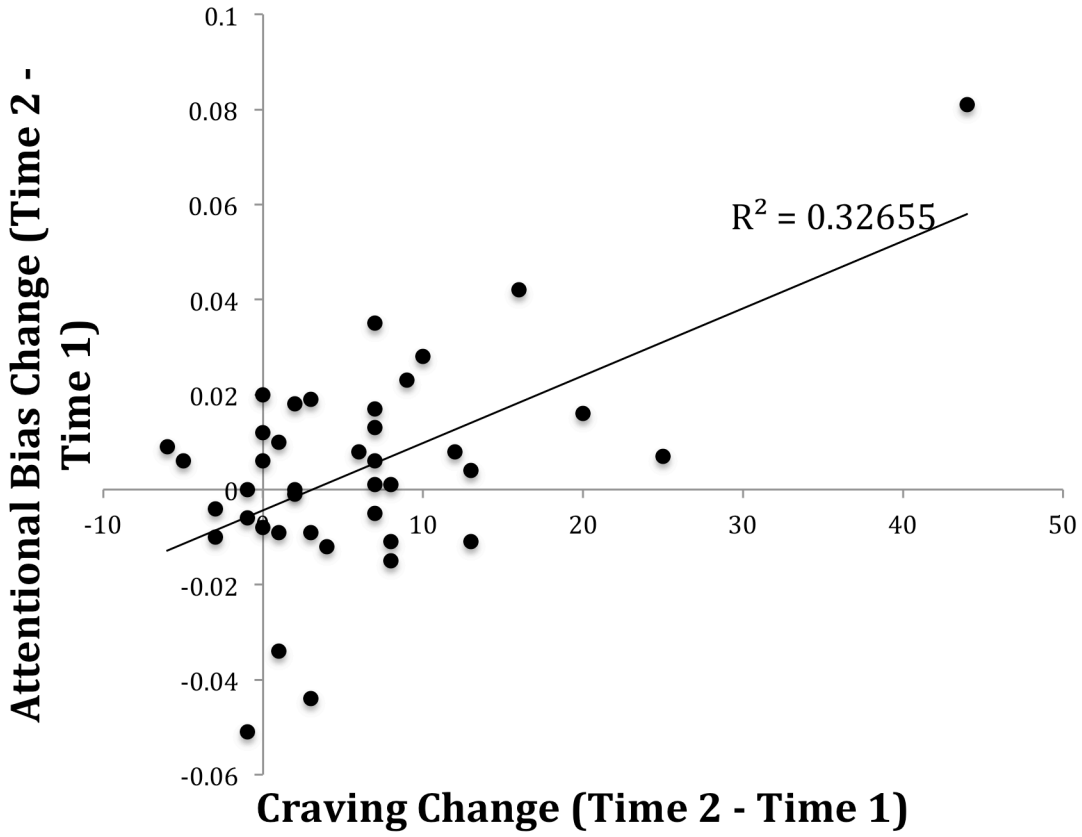

Figure 13. Group Long's within-session changes in craving (AUQ scores) predicting within-session changes in attentional bias (milliseconds). Change scores were quantified by subtracting values obtained during Time 1 from values obtained at Time 2 with positive scores indicating greater attentional biases and craving at Time 2. The best fitting line is illustrated.

Discussion

Experiment 3 utilized a between-groups design to examine the effects of extended alcohol cue exposure on subjective craving and attentional bias to alcohol among underage, college student drinkers. Several prominent results were obtained. First,

exposure to *in vivo* alcohol cues increased subjective reports of craving across both groups further replicating strong alcohol cue reactivity effects within this population of drinkers. Second, mean levels of craving at the end of the cue reactivity procedure were similar for both groups, however Group Short contained a significantly greater proportion of peak craving responders at the end of the CR procedure compared to Group Long. Upon further inspection, a subset of craving responders emerged from Group Long, those who reported peak craving at the end of the cue reactivity procedure and those who reported reductions in craving as predicted. Of critical importance, these subgroups of craving responders also differ on the basis of attentional bias to alcohol cues, with those reporting peak craving also exhibiting significantly stronger biases to alcohol cues. The finding that within-session differences in craving predicted corresponding within-session differences in attentional bias further supports the relationship between craving and attentional bias within Group Long. Like Experiment 2, these results are consistent with a core assertion of Franken's (2003) attentional bias model that drug craving should positively predict attentional bias to drug cues.

Consistent with past research and Experiments 1 and 2, the current results include robust overall increases in subjective craving following exposure to *in vivo* alcohol cues for both groups. This robust effect indicates cues as potent elicitors of craving among underage drinkers. To the degree that cue–elicited craving reflects a learned mechanism, the results suggest that craving responses develop among underage drinkers with presumably less drinking experience than their adult counterparts. Baseline rates of craving correlated with the number of years since participants first consumed alcohol suggesting that craving in general is greater for those with longer histories of alcohol use.

Baseline craving in this sample also significantly correlated with two measures of alcohol-related problems and baseline rates of drinking thus that those with more alcohol-related problems and greater reports of baseline drinking frequency and volume reported higher levels of craving at baseline.

The effects of extended exposure on craving partially aligned with the experimental hypotheses. Both groups reported similar mean levels of craving at the end of the CR procedure, however Group Short contained a significantly greater proportion of participants who reported peak craving. In other words, peak craving was reported more frequently at the end of the CR procedure when the alcohol cue exposure period was relatively short. Group Long, whose alcohol cue exposure period was three times longer than Group Short, exhibited considerable variation in craving at the end of the CR procedure indicating two subsets of individuals, those who reported peak craving after Block 6 (n = 17) and those who did not report peak craving after Block 6 (n = 23).

Previous studies have also identified subgroups of alcohol drinkers on the basis of varied craving responses. For example, Oslin et al. (2009) measured daily ratings of craving in alcohol-dependent individuals (N = 95) in treatment and found subgroups of individuals who reported high levels of craving throughout treatment (n = 17), individuals who reported initial elevations in craving followed by a decline (n = 37), and those who reported low craving throughout treatment (n = 41). In reactivity paradigms, participants have sometimes been classified as responders and non-responders with regards to both subjective craving and physiological activity (Szegedi et al., 2000). However, individual differences in craving response to extended alcohol cue exposure have not been explored. In the current study, the subgroups of craving responders did not

differ on the basis of alcohol-related problems or baseline rates of drinking, although the sample sizes were reduced when comparing subgroups and warrants future attention with larger samples. It would be of further interest to examine if craving eventually decreases for those who reported peak craving at the end of the CR procedure, or if these individuals maintain peak levels of craving for greater periods of extended cue exposure.

The effects of alcohol cue exposure on attentional biases to alcohol among Group Short are consistent with Experiment 2. That is, exposure to *in vivo* alcohol cues strengthened subsequent attentional biases to alcohol cues presented in the visual probe task. The effects of extended alcohol cue exposure on attentional biases to alcohol align with the observed variation among the subgroups of craving responders in Group Long. Of critical interest to the experimental aims, these subgroups not only differed with regards to self-reported craving, but also in independent measures of attentional bias to alcohol. For the subgroup of individuals who reported peak craving upon completion of the CR procedure, these individuals exhibited an increase in attentional bias to alcohol cues after the CR procedure. Individuals who did not report peak craving at the end of the CR procedure exhibited significantly weaker attentional biases to alcohol than those with peak craving. Furthermore, the attentional bias was numerically weaker after cue reactivity than at baseline for this subgroup. These subgroup differences are reflected by within-session changes in craving positively predicting within-session changes in attentional bias for Group Long indicating a relationship of moderate strength.

Despite the positive association between craving and attentional bias in Group Long, this association was not present among Group Short. The methodological difference between these groups may explain why the magnitude of effect size was

smaller in Group Short. Although a large proportion of participants in Group Short reported peak craving at Time 2, these reports of peak craving would likely continue to increase for some and decrease for others as suggested by the pattern of responding in Group Long. However, determining these directions is not possible without adding more blocks of alcohol cue exposure. The extended alcohol cue exposure period for Group Long allowed for the subgroups of craving responders to differentiate more clearly, and for this reason craving reported at Time 2 may be more stable for Group Long than for Group Short. In other words, we might be better able to predict if craving is increasing or decreasing at Time 2 for Group Long. If craving predicts attentional bias as posited by Franken (2003), we would expect the measurement of this relationship to be stronger when there is less fluctuation in craving.

In summary, *in vivo* alcohol cue exposure increased subjective craving and strengthened attentional biases to alcohol cues presented in a visual probe task. For participants that received extended alcohol cue exposure, subgroups of craving responders emerged with some showing reductions in craving as hypothesized, and others reporting peak craving at the end of the extended cue exposure period. Of critical importance to the experimental aims, these subgroups not only differed on the basis of craving but also on the independent measure of attentional bias to alcohol. For those that did report peak craving, attentional biases to alcohol were significantly stronger than those who reported declines in craving. This experiment provides further support for a positive relationship between craving and attention as predicted by Franken's attentional bias model (2003).

CHAPTER 6: OVERALL DISCUSSION AND CONCLUSIONS

Overview of experiments in relation to study aims

In this dissertation, I examined alcohol cue reactivity effects on craving and attentional bias among underage drinkers. This set of studies set out to accomplish several aims. First, I was interested in examining momentary craving and its predictive relationship with drinking outcomes. I accomplished this in Experiment 1 by using ecological momentary assessment (EMA) methods to capture craving reports randomly throughout the day in underage drinkers' natural environments. Craving reported throughout the day was used to prospectively predict subsequent drinking outcomes in the same social day.

The use of EMA in Experiment 1 also allowed me to examine alcohol cue reactivity in the natural environment. Specifically, alcohol visibility was modeled to predict craving while controlling for a number of other variables thought to influence craving among underage drinkers (e.g., peer presence, weekend status). Cue reactivity in the natural environment was then compared to *in vivo* alcohol cue reactivity in the laboratory in Experiment 1, while Experiment 2 and 3 also included lab-based cue reactivity to further demonstrate cue exposure effects on subjective craving.

Experiments 2 and 3 extended previous work on alcohol cue reactivity beyond studying effects on subjective craving by examining the effects on attentional bias to alcohol. Further, the relationship between craving and attentional bias was studied in each of these studies to test the assertion of Franken's attentional bias model (2003) that these two constructs should be positively correlated. Finally, all three studies included

individual difference measures of alcohol-related problems and baseline rates of drinking to explore potential predictors of craving and attentional bias to alcohol.

Craving and drinking outcomes

Conflicting findings regarding the relationship between craving and actual drug use outcomes are prevalent in the substance abuse research literature. Many of the studies that fuel this debate utilize varying methodologies and target conceptually distinct research questions. To date, most of the empirical evidence that demonstrates little or no positive relationship between craving and drug use measures include global measures of craving and measures of drinking outcomes assessed retrospectively over extended periods of time (for review, see Tiffany & Conklin, 2000). These studies however, do not inform us of the real-time relationship between craving and drug use. As methodological advances allow for measurement of these constructs without relying on retrospective recall, a clearer picture has emerged in which increased momentary craving positively correlates with drug use outcomes (Chandra, Scharf, & Shiffman, 2011; Litt, Cooney, & Morse, 2000). Experiment 1 was the first study to explore the relationship between momentary craving and subsequent alcohol use among underage drinkers. This study supports craving as a clinically meaningful construct in that higher daily averages of craving significantly predicted greater volumes of subsequent alcohol consumption in the same social day.

Although the primary aim of the dissertation was to examine the real-time relationship between momentary craving and drinking outcomes, all of the studies also included data to examine the relationship on a between-individual basis as previous studies have done. More specifically, these studies can assess whether individuals who

exhibit more craving in the natural environment or lab also report greater levels of recent drinking as measured by drinking consumption in the 90 days preceding a study visit. In the current set of studies, when significant effects were found, they were all in the direction to suggest that those who drink more also exhibit greater craving. Experiment 1 found that the percent of drinking days reported at baseline positively predicted craving reported in the lab, but did not predict the likelihood or intensity of craving experienced in the natural environment. Experiment 2 did not find a significant relationship between measures of baseline drinking and craving reported either during alcohol or water sessions. However, in Experiment 3, there was a positive correlation such that those who reported greater baseline drinking also reported more craving at the beginning of the cue reactivity.

Cue effects on craving

Another primary aim of the dissertation was to examine alcohol cue reactivity in underage drinkers' natural environments. Experiment 1 found that alcohol visibility reported in the natural environment was a significant predictor of momentary craving. Specifically, when alcohol was reported as visible there was a greater likelihood of experiencing craving and greater intensity of craving when it was experienced. Although the use of EMA to study this relationship in the natural environment provides strong advantages, there is also a lack of control characteristic of lab-based paradigms. For example, the natural environment includes other factors that may correlate with alcohol visibility and also influence craving. To control for this, the effect of alcohol visibility was tested in a model that included the effects of other potential influences on craving including peer presence, weekend status, and time of day. Above and beyond the effects

of these variables, alcohol visibility significantly predicted craving thus providing the first reported display of alcohol cue reactivity in the natural environment among underage drinkers.

A secondary aim of the studies was to replicate lab-based alcohol cue reactivity effects on subjective craving among underage drinkers. Cue reactivity effects on craving and related brain regions have been shown among adolescents, particularly those with AUDs or with greater drinking histories (Curtin et al., 2005; Tapert et al., 2003; Thomas, Drobes, & Deas, 2005). All three of the current studies found robust increases in subjective craving following *in vivo* alcohol cue exposure when compared to water cue exposure (Experiments 1 and 2) or baseline levels of craving following a rest period (Experiment 3). To date, the only other underage drinking study to measure physiological effects of cue reactivity failed to find an effect (Thomas, Drobes, & Deas, 2005), and Experiment 1 did not find significant cue effects on either heart rate or blood pressure. Overall, the current studies add to the body of cue reactivity research among underage drinkers, and also support the ecological validity of lab-based paradigms in that cue-elicited craving in the lab predicted cue-elicited craving in the natural environment as observed in Experiment 1.

Previous studies have found greater craving reported among adolescents with AUDs and greater drinking histories (Curtin et al., 2005; Tapert et al., 2003; Thomas, Drobes, & Deas, 2005). The current studies did not assess AUD status although scores on the AUDIT and RAPI suggest that these study samples reflect underage drinkers who report moderate levels of alcohol-related problems indicative of harmful drinking (Bohn et al., 1995) with sample means that are consistent with nonclinical adolescent drinkers

(White et al., 1988). Further, the majority of participants reported alcohol-related problems at levels considered to be below a severe threshold characteristic of underage drinkers with AUDs. Therefore the current study samples are unable to compare underage drinkers with and without AUDs. With this caveat in mind, Experiment 1 demonstrated that participants with higher RAPI scores showed greater cue-elicited increases in craving in the natural environment, although this effect was not replicated in the lab. In Experiment 2, neither RAPI nor AUDIT scores significantly correlated with craving reported after alcohol cue exposure although the direction of these correlations was positive in each case (r = .24 and r = .21 respectively). In Experiment 3, both RAPI and AUDIT scores significantly correlated with peak craving reported in the cue reactivity procedure for Group Short (r = .33 and r = .31 respectively) and Group Long (r = .39 and r = .36 respectively). Overall, those with more alcohol-related problems reported more cue-induced craving although this effect did not meet the threshold for significance in all studies. Treatment implications for this pattern of results are discussed below.

Cue effects on attentional bias to alcohol

Experiments 2 and 3 examined alcohol cue exposure effects on attentional bias to alcohol. Both experiments found that exposure to *in vivo* alcohol cues resulted in strengthened biases to alcohol cues presented in visual probe tasks. In Experiment 2, biases to alcohol cues were stronger following alcohol cue exposure as compared to water cue exposure in a separate session. In Experiment 3, biases to alcohol cues were stronger for both groups following alcohol cue exposure compared to baseline attentional biases measured in the same session. Increases in attentional biases to alcohol have been

previously observed following stress induction (Field & Powell, 2007), priming doses of alcohol (Schoenmakers, Wiers, & Field, 2008), and when in alcohol-associated contexts (Cox, Yeates, & Regan, 1999). The current studies are the first to show that exposure to *in vivo* alcohol cues also has a similar effect on attentional bias.

It is important to note that participants did not exhibit significant attentional biases to alcohol following water cue exposure in Experiment 2, or at baseline in Experiment 3. Under control conditions, attentional biases to alcohol have been previously observed among abstinent alcoholic adults (Bauer & Cox, 1998; Johnsen et al., 1994; Stetter et al., 1995; Stormark et al., 1997), alcoholic adults not receiving treatment (Stormark et al., 2000), heavy drinking college students (Townshend & Duka, 2001), and problem drinking college students as defined by those scoring 8 or greater on the AUDIT (Sharma, Albery, & Cook, 2001). The current set of studies included participants who scored below 8 on the AUDIT and who would not meet previous criteria for heavy drinking. This may explain why attentional biases to alcohol were not observed at the group level under control conditions. However, in both Experiments 2 and 3, attention was significantly biased to alcohol after participants had undergone *in vivo* alcohol cue exposure in each study. Therefore, nonclinical underage drinkers may represent a group of drinkers who do not reliably express attentional biases to alcohol, but are susceptible to changes in attention, such that attention becomes biased when exposed to cues that elicit craving.

Craving and attentional bias

Given that alcohol cue exposure increased subjective craving and strengthened attentional biases to alcohol, there is a possibility that craving mediates the relationship

between alcohol cue exposure and attentional bias. Franken's attentional bias model (2003) makes this prediction in that initial attention paid to alcohol cues results in increased craving, which in turn strengthens attentional biases to alcohol. A resulting positive feedback loop should be reflected in a predictive relationship between craving and attentional bias to alcohol. Regression analyses run in Experiments 2 and 3 support this predicted positive relationship. Within-subject differences in craving positively predicted within-subject differences in attentional bias in Experiment 2 ($r = .31$, $r^2 = .09$, $p = .054$) and for Group Long in Experiment 3 ($r = .57$, $r^2 = .33$, $p < .001$). Effect sizes of this relationship generally resembled or surpassed the significant but small positive relationship ($r = .19$ overall, $r = .23$ in high craving conditions) found in a meta-analysis examining craving and attentional bias (Field, Munafo, & Franken, 2009). Also, the subgroups of craving responders to extended alcohol exposure exhibited significant differences in attentional bias to alcohol in a direction consistent with Franken's model (2003). That is, those who reported peak craving at the end of extended alcohol cue exposure exhibited increases in attentional bias, while those who reported reductions from peak craving exhibited significantly weaker attentional biases.

On balance, the dissertation results support Franken's model (2003) in that craving and attentional bias to alcohol were consistently positively associated. However, the fact much of the variance in attentional bias is not explained by craving is somewhat problematic. Methodological limitations, like the use of indirect measures to assess attention have been previously discussed, and may have attenuated observed effects. Further, the attentional bias model may provide a better explanation of craving and attentional bias among more severe populations of drinkers. However, if future research

shows that craving positively predicts attentional bias to alcohol but leaves much of the variance unexplained, a central aspect of Franken's model (2003) may require modification. Future studies are recommended to utilize direct measures of attention such as eye-tracking procedures to improve the precision in measuring the relationship between craving and attentional bias to alcohol.

Other conditioning theory implications

The combined results have several important implications for theories that posit craving as a central marker of alcohol use. However, it is important to note that the theories to be discussed were developed to explain addictive behavior. Given that most of the study participants in the current sample report alcohol-related problem scores below thresholds thought to indicate alcohol dependence, it is unfair to judge these theories on the basis of the current findings. Instead, given that we know underage drinkers report craving and particularly in response to alcohol cues, the following is an attempt to examine other theoretical predictions that might improve our understanding of the underlying mechanisms of problematic, underage drinking.

First, the results from Experiment 1 support the shared theoretical prediction that craving is a mechanism that motivates alcohol-seeking and consumption behavior. Daily averages of craving predicted subsequent volumes of alcohol consumption in the same social day. Second, the results support the prediction that exposure to alcohol cues results in increased craving (Franken, 2003; Robinson & Berridge, 1993; Stewart, de Wit & Eikelboom, 1984; Wikler, 1948). The studies however, were not designed to distinguish the experience of craving as either a desire to alleviate withdrawal or a desire to experience the positively reinforcing effects of alcohol. However, it seems unlikely

that the participants would describe craving as relating to withdrawal given that only four participants (2.5%) across all three studies reported any withdrawal in the last three months as assessed in the RAPI. It is more likely that underage drinkers in these studies crave the positive and reinforcing effects of alcohol. It remains possible however, that underage drinkers with AUDs who report alcohol withdrawal are more likely to experience craving due to negative reinforcement mechanisms. The current studies did not assess AUD status and as such, experiential differences in craving warrant future research in this age group.

Although Tiffany's cognitive processing model (CPM, 1990) does not address cue reactivity in particular, this model asserts that craving should be present when automatic alcohol-seeking and consumption behaviors are interrupted. The nature of the cue reactivity protocol exposes participants to alcohol while blocking access to consumption. Therefore, the cue reactivity results do not contradict Tiffany's theory, as craving is predicted to increase under these scenarios. The finding that increased craving predicts greater alcohol consumption in Experiment 1 is generally not a prediction made by Tiffany's CPM. However, underage drinkers presumably face more obstacles in executing alcohol-seeking and consumption behavior given the illegal nature of their drinking. If underage drinkers are more likely to rely on controlled cognitive processes to obtain and consume alcohol, Tiffany's CPM would predict greater craving preceding drinking episodes. This can be partially examined by exploring the interactive effect of alcohol visibility and availability on craving reported in the natural environment in Experiment 1 to see if craving is greatest when alcohol is visible (cue exposure) but unavailable (access to consumption is blocked). Indeed, the average level of craving

reported when alcohol was visible but unavailable was 5.2 compared to 3.3 when alcohol was visible and available. Unfortunately, the relative infrequency of reports in which alcohol is reported as visible but not available (n = 13, ~2% of reports) limits the interpretation of this mean difference. However, these high craving reports are consistent with lab-based reactivity paradigms demonstrating that craving among young adults (ages 21-26) is greatest when alcohol is visible but perceived as unavailable (MacKillop & Lisman, 2005).

Public health and treatment implications

The current studies show that craving positively predicts alcohol consumption among underage drinkers and that the presence of alcohol cues positively predicts the likelihood and intensity of craving. With the intention of minimizing underage binge drinking, prohibiting alcohol paraphernalia in establishments or public places frequented by adolescents may help eliminate a significant source of craving. For example, while many colleges have banned alcohol on campus, some have banned the presence of all alcohol-related paraphernalia. The current studies suggest that students would experience less cue-elicited craving on dry campuses, and ideally reduce rates of alcohol consumption. Indeed, previous research has found that the heaviest sites for college student drinking include fraternity/sorority parties, off-campus bars, and off-campus parties where there are no prohibitions on the presence of alcohol or alcohol cues (Harford, Wechsler, & Seibring, 2002). It is unknown if these patterns may be explained by the mere differences in alcohol availability across settings or if students on campuses that prohibit alcohol and alcohol paraphernalia also report less craving for alcohol.

The current research also implicates treatments targeting reductions in craving as effective options for treatment-seeking underage drinkers. Recent pharmacological research has shown that naltrexone reduces the likelihood of drinking and heavy drinking days in underage drinkers, while also attenuating craving as measured both in the lab and natural environment (Miranda et al., 2013). Given that Experiments 1 and 3 provide evidence that those who report more alcohol-related problems experience more craving in response to alcohol cues, treatments that attenuate cue responses might be particularly beneficial for these problematic drinkers. Once such area of treatment, cue exposure therapy (CET), is similar to extended periods of exposure in cue reactivity paradigms while ensuring that patients are abstinent from alcohol. The logic underlying CET is that repeated, nonreinforced presentations of alcohol stimuli will eventually result in extinction learning. That is, in the absence of the reinforcing and subjective effects of alcohol, craving and other conditioned responses to alcohol stimuli will extinguish over time. Unfortunately, CET has not shown superior efficacy over other general forms of treatment to date (Martin, LaRowe, & Malcolm, 2010). However, principles of classical learning theory suggest CET may be improved with modifications. For example, CET is based on principles of extinction learning, and a large body of evidence shows that this type of learning is especially context-specific (Bouton, 2004). Therefore, extinction learning that occurs in a single and artificial context (e.g., hospital room) is unlikely to generalize to settings where alcohol use is common and where a renewal of conditioned responding would be expected. If concerns like this are addressed, and cue exposure therapies improve, reductions in cue-elicited craving may benefit those underage drinkers who report a number of alcohol-related problems.

There has also been recent interest in treatments that retrain attentional biases away from alcohol. Some of these retraining procedures utilize visual probe tasks as used in Experiments 2 and 3, except that probe cues consistently replace the location of neutral cues resulting in biases away from alcohol cues (Attentional Bias Modification Training, ABM). Recent research demonstrates that such treatments are effective at decreasing attentional bias towards alcohol cues (Schoenmakers et al., 2010) and that harmful drinkers exhibit post-training reductions in alcohol consumption with improvements still evident at a 3-month follow-up (Fadardi & Cox, 2009). The benefits of these treatments may not apply to the current population of drinkers given that participants did not exhibit significant attentional biases to alcohol following water cue exposure (Experiment 2) or at baseline (Experiment 3). Further, attentional biases did not correlate with alcohol-related problems or baseline alcohol use in a consistent manner across studies. However, in both studies, attentional biases to alcohol cues were observed immediately after exposure to *in vivo* alcohol cues, and as discussed earlier these biases were partially explained by increases in craving. It would seem more appropriate in this population to retrain attentional biases in situations when craving is expected to be high. Perhaps then, attentional retraining could occur in conjunction with CET, with the combined goal of reducing craving and retraining biases away from alcohol cues.

Study limitations

There are several general limitations to discuss regarding the studies beyond the specific limitations discussed in each study's discussion section. The most pressing is with regards to discrepancies in study sample characteristics between experiments. All three studies include similar proportions of males and females and have comparable mean

ages (18.5, 19.1, and 19.1 for Experiments 1, 2, and 3 respectively). However there are important differences to note. Compared to the age range in Experiments 2 and 3 (18-20 years old), Experiment 1 included a greater age range of participants (15-20 years old), although of the forty-two participants in the study sample only four participants were under the age of 18. Also, Experiment 1 included a mix of college students and individuals who were not attending college. Experiments 2 and 3 included samples entirely made up of college students. Although both college students and non-students of college age exhibit increased patterns of excessive drinking compared to adults, longitudinal data has shown that when compared to non-students, college students report lower rates of heavy drinking before college, but higher rates of heavy drinking during college (O'Malley & Johnston, 2002). Despite this difference, the main effects in Experiment 1 were consistent when analyzing college students and non-students separately. That is, craving predicted drinking, and cues predicted craving in underage drinkers regardless of student status. However, because of the sample characteristics in Experiments 2 and 3, the extent to which alcohol cue effects on attentional bias generalize to underage drinkers who are not college students remains unknown and warrants future attention.

Budgetary and time constraints resulted in methodological limitations regarding the cue reactivity protocol. For Experiments 2 and 3, *in vivo* alcohol cues were limited to several beer selections. As a result, participants were only eligible for the study if they reported drinking beer on at least a weekly basis for the past month. Although this criterion does not ensure that participants drank beer more than any other type of alcohol, the sample is limited to those who at least drink beer on a regular basis. Also, ideal cue

reactivity procedures are carried out on a day of the week and a time of the day that a participant usually consumes alcohol, however this was not always the case in the current studies. Instead, the cue reactivity procedure was run on all days of the week and at various times past 1pm in the afternoon. These limitations would be of a greater concern if the studies failed to show robust cue effects on craving in the current studies, however this was not the case. Further, the subgroups of craving responders in Group Long of Experiment 3 were examined to see if they could be differentiated on the basis of time of day or day of week of the study visit. Both subgroups included participants that underwent cue exposure at all times in the afternoon and early evening with median session start times of 3:00pm and 3:19pm for Group Long Decrease and Group Long Peak, respectively. Day of week also did not appear to differentiate these groups as 46.5% of participants in Group Long Decline and 39.4% of participants in Group Long Peak participated on a Thursday or Friday. Although these factors do not account for the difference in craving responses among Group Long, whether cue effects are modulated by day of week or time of day are important considerations for lab-based paradigms.

Future directions

There are several other further directions of research that could extend the current findings. First, given that craving can be conceptualized as a conditioned response, it would be worthwhile to explore the relationship between drinking history and craving. History of alcohol use information was only collected in a subset of the participants in Experiment 3 (n = 38), although there was a positive correlation between years since first alcohol use and craving. More research is needed to confidently determine if craving responses are stronger among those with greater drinking histories and a greater number

of conditioning trials. However, given that underage drinkers in the current studies reported robust increases in craving compared to adult drinkers (Carter & Tiffany, 1999), this suggests overall that participants have a sufficient amount of drinking experience for strong craving responses to emerge. Perhaps a more pressing question would be to determine how much drinking experience is necessary for craving responses to develop. This could be accomplished in a longitudinal manner to observe the temporal distance between the onset of drinking and the onset of subjective craving reports for alcohol.

Another area of interest is the influence of peers on alcohol craving among underage drinkers. In addition to alcohol visibility, the presence of peers was a significant predictor of craving intensity in underage drinkers' natural environments in Experiment 1. The conceptualization of alcohol cues sometimes extends beyond that of discrete or proximal cues (e.g., ads, paraphernalia) or alcohol itself. For example, Conklin and colleagues have described peers as representing "distal cues," and have shown that cigarette smokers experience greater craving in response to pictures of people with whom they regularly smoke (Conklin et al., 2013). The relationship however between peers and craving for alcohol is not well established, although there is evidence to suggest better social support is associated with greater craving for alcohol in adults (Chakravorty et al., 2010) and being at a friend's house is predictive of craving in treated, adult alcoholics (Litt, Cooney, & Morse, 2000). Additionally, adolescents have been shown to imitate their peer's drinking behavior during a drinking episode (Larsen et al., 2010). The current findings demonstrate the potential for peers to not only influence alcohol consumption directly, but also to influence craving for alcohol. Given that adolescence is characterized as a period of development in which peer relationships

become increasingly important, future lab-based studies could assess craving in response to peer presence, and also craving in response to alcohol cues as modulated by the presence of peers.

Finally, although Experiments 2 and 3 found that alcohol cue exposure strengthens attentional biases to alcohol, the momentary relationship between attentional bias and actual alcohol use was not examined. Previous research suggests a link between attentional bias and alcohol consumption rates (Field et al., 2004; Sharma, Albery, & Cook, 2001; Townshend & Duka, 2001), but much like the work on craving and alcohol use, this relationship has not been examined in real time or in the natural environment. Also, research in this area treats attentional bias to alcohol as a static measure, not one that fluctuates as shown in Experiments 2 and 3. As a result, future EMA research may determine if greater momentary attentional bias to alcohol predicts larger quantities of subsequent alcohol use, and if so, whether attentional bias explains unique variance in drinking or if this variance is accounted for by momentary craving. This could be done using methods similar to Experiment 1 with the inclusion of visual probe tasks on EMA devices to be delivered randomly throughout the day and also before and during drinking episodes. If momentary increases in attentional bias to alcohol predict subsequent drinking at the individual level, this would lend further support to treatments aimed at reducing these biases.

Concluding remarks

Underage drinking is a serious public health concern in the US in that there are a number of harms and negative consequences directly attributed to underage drinking (SAMSHA, 2007), and also because earlier ages of drinking onset are associated with

more severe alcohol problems later in life (Dawson et al., 2008). Although conditioning models of alcohol craving and attentional bias have been tested among adult alcoholics, the present research shows that these are clinically meaningful constructs among underage drinkers as well. Specifically, this dissertation demonstrated craving's predictive relationship with subsequent drinking in underage drinkers, while also demonstrating that alcohol cues elicit craving and strengthen attentional bias towards alcohol as hypothesized by Franken's attentional bias model of drug use (2003). Further, evidence that underage drinkers who reported more alcohol-related problems also reported greater increases in craving in the presence of alcohol cues suggests that cue-elicited craving may represent a viable pharmacological or behavioral target for intervention. Public health prevention and treatment research will greatly benefit from continued research elucidating the internal mechanisms that contribute to excessive drinking among those under 21 in the United States.

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