IMPAIRED CONTROL OVER ALCOHOL CONSUMPTION: LABORATORY AND FIELD INVESTIGATIONS

by

Joanna R. Sells

Dissertation submitted to the Faculty of the
Medical and Clinical Psychology Graduate Program
Uniformed Services University of the Health Sciences
In partial fulfillment of the requirements for the degree of
Doctor of Philosophy, 2019

Distribution Statement

Distribution A: Public Release.

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UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
SCHOOL OF MEDICINE GRADUATE PROGRAMS
Graduate Education Office (A 1045), 4301 Jones Bridge Road, Bethesda, MD 20814

APPROVAL OF THE DOCTORAL DISSERTATION IN THE DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

Title of Dissertation: "Impaired Control over Alcohol Consumption: Laboratory and Field Investigations"

Name of Candidate: Joanna Sells
Doctor of Philosophy Degree
June 11, 2019

DISSERTATION AND ABSTRACT APPROVED:

DATE:

[redacted] 6-11-19
Dr. Tracy Sbrocco
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Committee Chair

[redacted] 6-11-19
Dr. Andrew J. Waters
DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Dissertation Advisor

[redacted] 6-11-19
Dr. Patrick DeLeon
GRADUATE SCHOOL OF NURSING & DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY
Committee Member

[redacted] 6-11-2019
Dr. Vijay Ramchandani
NIAAA, NIH
Committee Member

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
SCHOOL OF MEDICINE GRADUATE PROGRAMS
Graduate Education Office (A 1045), 4301 Jones Bridge Road, Bethesda, MD 20814

FINAL EXAMINATION/PRIVATE DEFENSE FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN THE DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

Name of Student: Joanna Sells

Date of Examination: June 11, 2019
Time: 9:00 AM
Place: Room A2011

DECISION OF EXAMINATION COMMITTEE MEMBERS:

	PASS	FAIL
[redacted]	✓	
Dr. Tracy Sbrocco DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY Committee Chair		
[redacted]	✓	
Dr. Andrew J. Waters DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY Dissertation Advisor		
[redacted]	✓	
Dr. Patrick DeLeon GRADUATE SCHOOL OF NURSING & DEPARTMENT OF MEDICAL & CLINICAL PSYCHOLOGY Committee Member		
[redacted]	✓	
Dr. Vijay Ramchandani NIAAA, NIH Committee Member		

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Joanna Sells

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ABSTRACT

Impaired Control over Alcohol Consumption: Laboratory and Field Investigations

Joanna R. Sells, M.S., 2019

Thesis directed by: Andrew J. Waters, Professor, Medical and Clinical Psychology

Excessive drinking remains a significant public health problem in the US. A better understanding of the psychological processes underlying excessive drinking is needed so that more effective interventions can be developed. Recent research has focused on impaired control which can be defined as a failure to avoid drinking or to limit consumption once it has begun. To better understand the processes underlying impaired control, we developed an ecological momentary assessment (EMA) model to compare to a novel human laboratory model (Computer-Assisted Self-infusion of Alcohol or CASE) that assesses actual consumption behavior indicative of impaired control (Resist CASE: R-CASE). It is imperative that the model, (R-CASE), as well as the parent model (CASE), be tested against field data to ensure effective translation.

Heavy drinkers (N=16) were scheduled to complete a free-access CASE session as well as up two R-CASE sessions (one with a priming alcohol exposure and one without). Participants completed between two and six weeks of EMA (954 assessments) to assess motivation and drinking. The overall goal was to examine the validity of the lab models (CASE and R-CASE) in assessing impaired control over alcohol consumption. The specific aims were: 1) To examine the association between alcohol self-administration in the lab during the free-access (CASE) session (Lab Consumption) and drinking behavior

in the real-world, assessed using EMA; and 2) To examine predictors of drinking in the lab and field including impulsivity trait measures. In exploratory analyses, the association between ability to resist alcohol self-administration in the lab (Resist CASE) and the ability to abstain from drinking in the real-world, assessed using EMA, was examined, as were within-subject predictors of drinking in the field.

For Specific Aim 1, there was no evidence for an association between total alcohol consumed during free-access CASE and EMA alcohol consumption, and there was no moderation by motivation to abstain. For Specific Aim 2, unexpectedly, impulsivity and lab consumption of alcohol during the second visit with alcohol prime were negatively correlated. There was no evidence for an association between lab assessed perceived control or impulsivity measures including delayed discounting and EMA alcohol consumption. Exploratory analyses revealed that there was no evidence that ability to resist drinking in the lab was associated with drinking in the field. However, a number of within-subject predictors of drinking, including motivation to abstain from alcohol use, were identified.

In sum, this study provides preliminary data regarding feasibility of a lab-EMA paradigm of impaired control. Further research is required to validate the CASE and R-CASE models as human laboratory paradigms to assess impaired control over drinking.

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CHAPTER 1: ALCOHOL USE

Excessive alcohol use remains a significant public health problem in the US. Although evidence-based treatments for excessive alcohol use are available, most attempts to limit alcohol consumption end in failure and a return to former drinking patterns. A better understanding of the psychological processes underlying excessive drinking is needed so that more effective interventions can be developed. This dissertation focuses on the development of measures of impaired control.

This first chapter is organized as follows. First, given the large number of terms that are used to describe excessive alcohol use, an introduction to alcohol use and its terminology will be provided. Second, estimates of the prevalence of excessive alcohol use as well as the adverse economic effects will be reviewed. Third, the neurobiological effects of alcohol will be briefly described. Fourth, binge drinking, the focus of the present study, will be introduced, along with alcohol use disorders. Fifth, current treatments of excessive alcohol use will be reviewed. Last, it will be argued that new treatments for excessive drinking are required, and that a better understanding of the psychological processes underlying excessive drinking and relapse is required to develop more effective interventions.

NOTE ABOUT TERMINOLOGY

Alcohol use is prevalent in many societies, including across the U.S. Excessive alcohol use has been a major public health concern for decades. Culturally ingrained events such as happy hours, keg parties, military traditions (Ames & Cunradi, 2004-2005), wedding toasts, and wine tasting sanction and encourage drinking. Bars and liquor

stores in most counties in the US are easy to find, open early and/or late, and are profitable. $155 billion dollars of total net revenue/turnover was made by the 26 largest global alcoholic beverage companies in 2005 (Jernigan, 2009). The largest marketers of alcohol are 10 beer companies, who accounted for 48% of volume sales of global alcohol brands in 2005 (Jernigan, 2009).

Along with cultural and profit-driven encouragement of drinking comes mixed perspectives on alcohol use. There has even been a meta-analysis of 84 articles that found value in moderate drinking (e.g. 1-2 glasses of wine per day) for decreasing the risk of developing many cardiovascular conditions, despite the clear risks of alcohol use in many types of people (e.g. those with predisposition for and in recovery from alcohol problems) (Ronksley et al., 2011). This and related findings have been heavily covered on the news and in mass media, often with the suggestion that drinking 1-2 glasses of wine per day is beneficial to heart health (Penn State, 2017). However, the meta-analysis, which used data from 67 studies, has been called into question as several of the studies had poor methodology including lack of control for smoking or health status, limited assessment of drinking history, and, categorizing former drinkers as abstainers (Stockwell, Greer, Filmore, Chikritzhs, & Zeisser, 2012; Stockwell et al., 2016).

While popular and scientific opinion have evolved and continue to shift, so have the constructs and terminology of problem drinking. “Alcoholism”, which can also be thought of as the study of “alcoholics”, is no longer the politically preferred term. Moreover, use of the term “alcohol abuse” has been shown to increase person-blaming stigma, even among healthcare professionals (Kelly & Westerhoff, 2010). Many of the articles cited in this study used DSM-IV criteria for “alcohol dependence “and/or

"alcohol abuse", which were the dominant diagnostic terms used in treatment and research settings (American Psychiatric Association, 2000).

Alcohol dependence is the more severe end of the pathological alcohol use continuum, while alcohol abuse is worrisome, but not severe. "Alcohol misuse" is another term for alcohol abuse, but with the intended effect of minimizing moralistic blaming of those who drink heavily for their behaviors. When preparing this manuscript, the current DSM-5 terminology of "alcohol use disorder" (AUD) was used (American Psychiatric Association, 2013). AUDs range from mild to severe, likely capturing most people who might have met criteria for alcohol dependence and alcohol abuse in prior years. While using the term AUD has limitations, it is the current simplest way to aggregate terminology while also making efforts to reduce stigmatization of those suffering from the consequences of excessive alcohol use.

PREVALENCE AND EFFECTS OF ALCOHOL USE

The prevalence of alcohol dependence (now termed alcohol use disorder or AUD) increased 37.6% between 1990 and 2010, fueled in part by ageing and growing populations (Whiteford et al., 2013). Approximately 61% of Americans age 18 and over were current drinkers between 2005-2007 (Schoenborn & Adams, 2010). Alcohol consumption causes approximately 9.6% of disability-adjusted total life years lost and accounts for 44.4% of years of life lost due to mental and substance use disorders (Whiteford et al., 2013). It is the fifth leading cause of death, according to the 2010 Global Burden of Disease Study (Whiteford et al., 2013).

In a study of the economic impact of alcohol, alcohol use is defined as excessive if it is binge drinking (five or more drinks per occasion for a man and four or more drinks

per occasion for a woman), heavy drinking (more than eight drinks per week for women and more than 15 drinks per week for men), or alcohol use under age 21 or while pregnant (Sacks et al., 2015 as cited in Centers for Disease Control (CDC), 2017). A 2006 economic analysis forecasted for 2010 found that $249 billion dollars were lost annually in the US to excessive alcohol consumption (Sacks et al., 2015). In the 2010 projections, for every drink taken, the economic cost is $2.05 or $807 per person (Sacks et al., 2015 as cited in CDC, 2017).

The economic impact of excessive alcohol consumption on federal and state budgets estimated that governments paid for $100.7 billion of the $249 billion dollar costs (Sacks et al., 2015). Other breakdowns of the $249 billion dollar costs indicated that 76.7% was due to binge drinking, 9.7% was due to underage drinking, and 2.2% was associated with drinking while pregnant (Sacks et al., 2015). The study found that states had a 2010 projected annual median cost of $3.5 billion, with a range from $35 billion in California to $488 million in North Dakota (Sacks et al., 2015). The per person costs are highest in the District of Columbia, at $1,526 and lowest in Utah at $592 (Sacks et al., 2015). Costs were primarily related to decreased work productivity (at 72%), health care (at 11%), and involvement with the criminal justice system, motor vehicle crashes, and property damages (at 17%) (Sacks et al., 2015). The authors of the study also note the economic recession of the mid 2000s likely minimized the growth of the economic impact of excessive use of alcohol (Sacks et al., 2015).

The economic impact of excessive alcohol use, particularly with regards to treatment for AUDs is a strong rationale for studying binge drinking. Binge drinking can lead to the development of alcohol use disorder (AUD) and a host of consequences

associated with the disease, including cancer, liver cirrhosis, depressive episodes, insomnia, and suicide (NIAAA, 2012; Schuckit, 2009).

ALCOHOL USE AND HEALTH DISPARITIES

Consumption Patterns and Outcomes by Race and Ethnicity

Health disparities are differences in health outcomes among groups. In the U.S., where health care is not universally available, research has focused on differences in health care access and quality among racial and ethnic minorities relative to the White or Caucasian population (James et al., 2017). Most notably, in a report of a survey of U.S. adults that focused on rural versus urban health disparities across racial and ethnical groups, all racial and ethnic minority populations were less likely to have a personal health care provider (James et al., 2017). Intersectionality, a framework describing interlocking systems of power and oppression, is important to consider when exploring the important roles of racial, ethnic, and gender factors in drinking behavior and related health disparities (Crenshaw, K, 2018; Kulesza et al., 2016). The effects of acculturation and use among different racial and ethnic subgroups are understudied, but important considerations when examining disparities in alcohol use, related health outcomes, and differences in outcomes when consumption patterns are the same as other ethnic and racial groups (Zemore et al., 2018).

National alcohol consumption data from the 2007 National Survey on Drug Use and Health (SAMHSA, 2010) was reported by Delker, Brown, and Hasin in a 2016 review article. In this dataset, Whites had the highest alcohol consumption rates at 59.8 percent, followed by Native Americans/Alaska Natives at 47.8 percent, Hispanics at 46.3 percent, Blacks at 43.8 percent, and Asian Americans at 38.0 percent (SAMHSA,

2010). In 2015, it was reported that among heavy drinkers aged 12 and over in minority groups, American Indian/Alaska Natives have the highest national rates at 9.2 percent, followed by non-Hispanic Whites at 7.1 percent, two or more races at 5.8 percent, Hispanics at 5.1 percent, Native Hawaiian or Other Pacific Islanders at 4.6 percent, and Asians at 2.0 percent (SAMHSA, 2015 September). However, a recent national survey found that Whites had the highest rates of binge drinking in the prior month, followed by Alaska Native and American Indian, Hispanics, Blacks, and Asians or Native Hawaiian or other Pacific Islander (James et al., 2017). Despite the increased binge drinking by Whites, factors involved in health disparities may help protect members of this racial group from negative outcomes from binge drinking.

While group and individual alcohol consumption levels are important to consider, even when consumption is low and/or equal to other groups, health outcomes often vary along racial and ethnic lines. For example, African Americans generally drink less in terms of an individual's frequency as well as less overall as a group when compared with Caucasians, but they have higher rates of drinking related problems (Zapolski et al., 2014). Specifically, a national survey of young adults between 18-25 found that African Americans were less likely to be a current, heavy, or binge drinker when compared to Caucasians (SAMHSA, 2010, 2011).

Further, African Americans have higher rates of alcohol abstention relative to Caucasians and those who report drinking report less frequently and smaller quantities of alcohol consumption (reported in Zapolski et al., 2014). Despite this data, African Americans have been shown to have higher incidence rates of hypertension and mortality from head and neck cancers that are linked to alcohol use (Zemore et al.,

2018). Continuing with the paradox of worse outcomes among groups with fewer and lighter drinkers, mortality from liver cirrhosis has been shown to be 1.27 times more likely (Buka, 2002) and mortality rates from alcohol related diseases and disorders have been shown to be 10% higher (Kochanek et al., 2004). While historically, along with African Americans, Latinos, and American Indians have had higher rates of liver cirrhosis, current data suggests that only Latinos and American Indians persist in this health disparity (Zemore et al., 2018). There is clearly more to the story of how alcohol consumption rates, culture, race, and ethnicity interact to contribute to health disparities.

The work of Zapolski et al. (2014) and Spillane and Smith (2007) as summarized in Zemore et al. (2018) examine these differences further. They suggest that health disparities may relate to the degree of availability of reinforcers such as housing, economic and work security, knowledge, and relationships within environmental and individual contexts. Similarly, Jackson and colleagues (2015) found that social integration, "the set of arrangements adopted by a society to accept new members" including variables such as employment, poverty, poor health, and education are key to understanding differences in health outcomes for the same drinking behavior between Blacks and Whites. These reinforcers become especially critical as young adults begin to interact as independent members of society with societal institutions such as post-secondary education and the workforce. The pressures and demands of this developmental stage may be part of the reason that young adults aged 18-25 have been found to have especially high risk of drinking related accidents and of developing alcohol use disorder (national datasets summarized by Delker, Brown, & Hasin, 2016).

Several groups of researchers (Chartier et al., 2014; Vaeth et al., 2017) have called for additional research to identify and examine risk and protective factors at the neighborhood level along with racial/ethnic, genetic, and other individual factors to help understand and address health disparities related to drinking behavior. Along with these factors, particular attention should be paid to the relationship between drinking and the developmental trajectory of young adults to identify and develop AUD prevention.

Consumption Patterns and Outcomes by Gender

Gender is another important factor in drinking behavior. Differences in alcohol use by gender have influenced gender roles in societies. Historically, alcohol use in women has been seen as pathological, while alcohol use in men has been seen as a normal (Wilsnack & Wilsnack, 1997). Recent data suggests that despite historical differences in how drinking has been viewed in women and men, drinking rates are often just as high in girls and women. Rates of alcohol use are similar in boys and girls in 8th grade (13% for girls, 12% for boys in the past 30 days). This difference grows by 12th grade, when 38% of female versus 42% of male students reported alcohol use in the prior 30 days (Johnston et al., 2013).

Once adulthood is reached, men consistently use higher rates than women (Johnston et al., 2013; Wilsnack et al., 2000). In a survey of 16 countries, including the United States and Canada, there were few differences in the probability of current drinking versus abstaining, when comparing men and women (Wilsnack et al., 2000). However, in terms of frequency and quantity of drinking, rates of heavy drinking episodes, and adverse drinking consequences, the rates for men exceeded the rates for

women (Wilsnack et al., 2000). Further, women were more likely to be lifetime abstainers (Wilsnack et al., 2000). In older age groups, all drinkers tended to drink smaller quantities of alcohol and all drinkers were more likely to stop drinking (Wilsnack et al., 2000).

Race, ethnicity, gender, and intersectionality among these and other factors are essential considerations for future research examining heavy drinking and the risk of developing AUD. Family structure and income may be particularly important when considering rates of alcohol consumption (Kerr, Patterson, & Greenfield, 2009). Excessive alcohol use and AUD has a devastating impact on families and communities. Given the data that shows age of onset of drinking is highly related to the development of AUD, the inter-generational effects of alcohol use and the social pressures to use alcohol, the developmental period of young adulthood holds special promise as a target for prevention and intervention development. Further, environmental and individual factors including social integration (Jackson et al., 2015) and intersectionality must be taken into account when examining etiology of drinking behavior and consumption patterns over time.

ALCOHOL AND THE CENTRAL NERVOUS SYSTEM

Ethanol is a molecule that readily distributes in the brain, with peak levels typically reached 30 minutes after drinking an alcoholic drink (Knapp, Ciraulo, & Kranzler, 2008). Alcohol is formed in the fermentation of ethanol sugars by yeast to a concentration of 15%, while distillation greatly increases this concentration (Masters, 2012). Distilled spirits have approximately 30-60% ethanol concentration, sherry/port and other fortified wines have 14-20%, wines have 11-14%, and beer has 4-10%. Ethanol

is water-soluble and small, leading to rapid absorption in the gastrointestinal tract within 30 minutes of ingestion (Masters, 2012). Ethanol is metabolized in two steps with the enzymes alcohol dehydrogenase and aldehyde dehydrogenase (Knapp, Ciraulo, & Kranzler, 2008). Effects of alcohol are generally proportional to the level of exposure (blood alcohol concentration or BAC). At BACs ranging from 50-100mg/dL, alcohol causes stimulation, the feeling of being "high," and slower reaction times (Masters, 2012). At 100-200mg/dL, alcohol impairs motor function, slurs speech, and leads to ataxia and sedation (Masters, 2012). At 200-300mg/dL, emesis and stupor are experienced (Masters, 2012). At 300-400mg/dL the drinker will experience a coma, and use at more than 400mg/dL, the result of alcohol use is respiratory depression and death (Masters, 2012).

Ethanol (or alcohol) concentration in the brain rises quickly following ingestion as it readily crosses biologic membranes, with tissue levels containing nearly equivalent concentration of ethanol in the blood (Masters, 2012). Alcohol exerts its effects on the central nervous system (CNS) through dopamine, norepinephrine, endogenous opioids, gamma-Aminobutyric acid (GABA), glutamate, and serotonin (McIntosh & Chick, 2004). GABA is the neurotransmitter responsible for most inhibition activity in the CNS, while glutamate is the most abundant neurotransmitter in the vertebrate CNS and is associated with the excitatory amino acid system (Myrick & Wright, 2008). Alcohol increases dopamine release in the mesolimbic system reward pathway, specifically affecting the nucleus accumbens, which is associated with the rewarding effects of alcohol use (Knapp, Ciraulo, & Kranzler, 2008).

Alcohol releases norepinephrine, which accounts for the uplifting and energizing clinical effects of alcohol use (McIntosh & Chick, 2004). Endogenous opioid stimulation by alcohol leads to the stress-reducing, pleasurable, and analgesic effects (McIntosh & Chick, 2004). As BAC rises, so does a rapid stimulation of GABA receptors, provoking inhibitory effects that lead to amnesia, sedation, and anxiolytic and ataxic responses of the brain (Knapp, Ciraulo, & Kranzler, 2008; McIntosh & Chick, 2004). The depressant effects of alcohol on the brain are primarily due to its blocking of glutamate or NDMA receptors, furthering amnesic effects, as the BAC decreases (Knapp, Ciraulo, & Kranzler, 2008; McIntosh & Chick, 2004). Finally, serotonin stimulation from alcohol use is responsible for nausea responses and may help explain the variety of alcohol user types- from aggressive to anxious (McIntosh & Chick, 2004).

While any level or frequency of alcohol use will impact the user's neuronal system, binge drinking is particularly risky. When binge drinking, a person is at risk of death through alcohol's suppression of brain stem nuclei necessary to regulate life sustaining reflexes such as gagging (Miller & Gold, 1991). Binge drinking is described in further detail below.

BINGE DRINKING

Binge drinking is a pattern of drinking that raises a person's blood alcohol concentration (BAC) to the legal limit of 0.08 g/dL, which translates to approximately four drinks for women and five drinks for men over the course of two hours (NIAAA, n.d. *Drinking levels defined*). Relatedly, the Substance Abuse and Mental Health Services Administration (SAMHSA) defines binge drinking as consuming four or more drinks for women or five or more drinks for men at the same drinking occasion or within a few

hours (SAMHSA, 2015 October). The term "binge drinking" was used to describe clinical symptoms of heavy drinking followed by abstinence (as opposed to heavy drinking, which may not rise and fall in frequency) (SAMHSA, 2015 October).

The current NIAAA standard of binge drinking (NIAAA, n.d. *Drinking levels defined*) were derived following a study (Wechsler et al., 1994) that provided an operationalized definition of binge drinking, with consideration for gender differences in metabolic rates, consumed over the prior two weeks (SAMHSA, 2016; Wechsler et al., 1994). The number five or more drinks for men and four or more drinks for women indicated the minimum amount of drinking typically associated with high-risk consequences of alcohol use including health, legal, and economic consequences (Wechsler, 1994). The 2009 National Survey on Drug Use and Health (NSDUH) found that among persons aged 12 or older, 23.7% engaged in binge drinking at least once in the prior 30 days (SAMHSA, 2010). The rates of binge drinking are highest in ages 18 to 25 with 41.7% of the U.S. population endorsing this high-risk type of drinking (SAMHSA, 2010).

A recent analysis of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) from 2001-2002 (NESARC I) and 2012-2013 (NESARC III) data examined changes in drinking patterns by demographics and factors including sex, race/ethnicity, employment status, marriage, having kids, college education, income, smokers, and drug use (Hingson, Zha, & White, 2017). The analysis created 3 groups based on below threshold binge drinking gender based categories. Relative to the below threshold respondents, Level I had binge drinking at 1-2 times higher, Level II had binge

drinking at 2-3 times higher, and Level III had binge drinking at 3 or more times higher than the below threshold respondents (Hingson, Zha, & White, 2017).

Binge drinking can lead to damage to the body, particularly to the brain and liver, the heart leading to hypertension, and in pregnant women, fetal damage (SAMHSA 2014; 2015, September; 2016). Binge drinking can lead to blackouts and overdoses as well as driving while intoxicated, risky behaviors such as high-risk sex, injuries, fighting, and other behaviors that may lead to legal problems (Hingson, Zha, & White, 2017; White, Hingson, Pan, & Yi, 2011). When binge drinking is combined with additional drug use, both legal and illicit, the consequences can be severe.

ALCOHOL USE DISORDER

Chronic alcohol use may develop into an alcohol use disorder (AUD). In order to be classified as having an alcohol use disorder, those with chronic use must exhibit three or more of the following within 12 months: tolerance; withdrawal; craving; recurrent use resulting in failure to fulfill major role obligations at work, school, or home; use in larger quantities or over longer periods of time than intended; persistent desire or unsuccessful efforts to cut down use; large amounts of time spent obtaining, using, recovering from use; reduction of important activities (social, occupational, recreational); recurrent use in physically dangerous situations; continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely caused or exacerbated by use; continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by effects of use (American Psychiatric Association, 2013). In terms of biological effects, chronic alcohol use impacts the liver as well as the nervous, gastrointestinal, cardiovascular, and immune systems, and can lead to death.

Chronic alcohol consumption deaths are typically a result of liver disease, cancer, accidents (car, falls, or otherwise), and suicide (Masters, 2012). Alcohol use disorder and substance use disorder are chronic, recurring conditions with stages of treatment, abstinence, and relapse throughout their time as a drinker (McKay & Hiller-Sturmhofel, 2011). Treatment of those with AUD in the U.S. is a monumental task that is currently insufficient to meet the growing needs of the population. Among 19 million Americans over age 12 who meet AUD criteria, as few as 12.1% received treatment in the prior year (Hasin, Stinson, Ogburn, & Grant, 2007). In Americans over age 12 who meet AUD criteria, only 24.1% ever receive treatment during their lifetime (Hasin, Stinson, Ogburn, & Grant, 2007). The NESARC survey authors also found that the mean age for initial AUD treatment was 29.8 years with an average 8-year lag between the onset of AUD and entry into treatment (Hasin, Stinson, Ogburn, & Grant, 2007). Of those with AUD for the past year (alcohol dependence, not alcohol abuse), 10.0% were treated by a health professional (excluding treatment by a clergy member, employee assistance program, or 12 step group), 7.4% were treated through 12-step self-help groups, 6.7% were treated by a health professional (Medical doctor, nurse practitioner, etc.…) (Hasin, Stinson, Ogburn, & Grant, 2007). Specific treatments for AUD are addressed below.

TREATMENT OF ALCOHOL USE DISORDERS

The NIAAA has recently developed a treatment navigator to assist those looking for treatment for their alcohol use (NIAAA, 2017) and provides tools and information for the consumer who is considering alcohol treatment (NIAAA, 2012). The navigator is designed to walk through behavioral, and pharmacological treatment options while also providing psychoeducation about alcohol use (NIAAA, 2017). For those with more

severe alcohol use disorder, alcohol withdrawal treatment, provided in inpatient and outpatient settings, is typically the first course of treatment (NIAAA, 2017). This treatment addresses nutritional deficits, particularly for thiamine, through administration of nutritional supplements (Myrick & Wright, 2008). Further, benzodiazepines are administered to treat withdrawal symptoms such as insomnia and anxiety, and to prevent grand mal seizures (Bisaga, 2008). Subsequent treatment options that address alcohol use disorders or maintenance of treatment outcomes include pharmacotherapy, psychotherapy, and self-help groups.

Several medications have been developed and are approved to treat AUD. These include naltrexone, acamprosate, and disulfiram (Myrick & Wright, 2008). Typically, these medications are used in the first twelve weeks of treatment, however extended treatment protocols are being studied (McKay & Hiller-Sturmhofel, 2011). Nalmefene, varenicline, and baclofen also hold promise for treating AUDs.

Naltrexone was approved to treat AUDs in 1994 after it was thought to reduce drinking frequency and likelihood of relapse (Myrick & Wright, 2008; NIAAA, 1995). It was the first treatment approved to treat AUDs in nearly 50 years (Croop, Faulkner, & Labriola, D. F., 1997). Naltrexone reduces the individual's subjective experience of pleasure from drinking alcohol and can reduce craving by acting as an antagonist on the endogenous opioid system in the brain (McKay & Hiller-Sturmhofel, 2011; Myrick & Wright, 2008). Naltrexone's mechanism of action is via blocking mu-opioid receptors thereby inhibiting dopamine release and the associated reinforcing effects of alcohol and associated cues (Myrick & Wright, 2008). Naltrexone performed favorably in the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) trial,

a randomized controlled trial of 1,383 persons with AUD who were abstinent (Anton et al., 2006). In COMBINE, participants were given naltrexone, acamprosate, both naltrexone and acamprosate, or both placebos, with or without combined behavioral intervention (CBI) or CBI without any medications (Anton et al., 2006). Naltrexone reduced the risk of heavy drinking days, and when combined with medical management or with medical management and CBI, along with CBI plus medical management and placebos, had a higher percentage of abstinent days (Anton et al., 2006).

Acamprosate was approved by the FDA in 2004 for the treatment of AUD, but it has been available in France since 1989 (Myrick & Wright, 2008). It is believed to help achieve balance of several signaling systems in the brain that are affected by alcohol, helping with abstinence maintenance and decreasing negative symptoms of withdrawal, however the exact mechanism of action is not well understood (McKay & Hiller-Sturmhofel, 2011; Myrick & Wright, 2008). It is believed to be a putative glutamate modulator and is structurally similar to GABA (Anton et al., 2006; Myrick & Wright, 2008). Many trials in Europe have demonstrated the safety and efficacy of acamprosate (Myrick & Wright, 2008), however the COMBINE intent to treat analyses did not support acamprosate's efficacy (Anton et al., 2006). These inconsistent results have been hypothesized to be due to varying study design including type of population and environment of treatment (e.g. inpatient versus outpatient) (Myrick & Wright, 2008).

Disulfiram has been used for over 50 years as a deterrent to drinking by reacting with alcohol to create an undesirable response (e.g. flushing, headache, nausea). This response is due to disulfiram blocking the breakdown of acetaldehyde to acetate (two substrates of ethanol) (Myrick & Wright, 2008). Theoretically, the conditioned pairing of

alcohol with uncomfortable symptoms will serve as a strong negative reinforcer for avoiding the consumption of alcohol. While disulfiram has shown some efficacy, it is particularly challenging to maintain patient adherence to the treatment (Myrick & Wright, 2008).

Since being approved by the European Medicines Agency in 2013, Nalmefene has become a treatment for patients with alcohol use disorders who have high risk drinking levels without withdrawal symptoms and who do not have critical detoxification needs (Muller, Geisel, Banas, & Heinz, 2014). It is an opioid system modulator with a similar structure to naltrexone (Muller, Geisel, Banas, & Heinz, 2014). However, according to a systematic review and meta-analysis, it still has limited efficacy support for reducing alcohol consumption (Palpacuer et al., 2015).

Baclofen, a GABA-B receptor agonist, was originally approved to treat spasticity (Muller, Geisel, Banas, & Heinz, 2014), but has become a popular treatment for AUDs in France. Part of the popularity of baclofen as a treatment for AUD stems from a case study written by a French cardiologist suffering from AUD who took high doses weekly for five weeks and maintenance doses for eight months (Ameisen, 2004).

Treatment for alcohol use disorders ranges from self-help groups to psychotherapy to medication therapy. Treatment may be provided in outpatient or in-patient settings. Often, an individual will engage in several different types of treatment over the lifetime of their alcohol use disorder. This may be due to their changing needs, changing severity, and unsatisfactory treatment response. Treatment response can be difficult to track over the long-term in part due to limited research resources and limited patient participation in after-care (McKay & Hiller-Sturmhofel, 2011). Treatment may

also be interrupted or stop due to limited funding for care, practical barriers such as limited transportation or lack of child care, high drop-out rates, patient ambivalence, or discomfort with treatment (McKay & Hiller-Sturmhofel, 2011). For example, some patients are not comfortable with the spiritual component of Alcoholics Anonymous and the emphasis on a higher power (McKay & Hiller-Sturmhofel, 2011). There are two schools of thought with regards to alcohol use disorder treatment; one uses the harm reduction model and one supports abstinence from alcohol.

Alcohol use disorders can also be treated with group therapy or individual therapy such as cognitive behavioral therapy (McKay & Hiller-Sturmhofel, 2011). The Minnesota Model is a popular and pervasive treatment that starts with an intensive inpatient treatment phase followed by less intensive outpatient care. The Alcoholics Anonymous (AA) principles, along with a holistic approach to treatment, are the basis for care. AA is also part of the outpatient portion of treatment. The Minnesota Model has been criticized for being inflexible to those who do not subscribe to AA principles (McKay & Hiller-Sturmhofel, 2011).

Self-help groups, such as Alcoholics, Narcotics, or Cocaine Anonymous, is another common option in supporting those with AUD and SUD. These are often not considered formalized treatment interventions (McKay & Hiller-Sturmhofel, 2011). These groups meet regularly and provide spiritual support, through the acknowledgement of a higher power, and behavioral guidance based on principles of abstinence and living a sober lifestyle. It also provides social support to people who are often ostracized by those who do not suffer from addictions (McKay & Hiller-Sturmhofel, 2011). Group meetings are run in cities and towns all over the world and each group of attendees has a culture

within the group. For example, meetings may focus on a certain age demographic or may be exclusive to gender or sexual orientation. Some meetings are open, where any member of the public can join and participate or observe, while others are closed to the usual group members. There are also self-help programs that do not focus on a higher power in their approach. These include SMART recovery, Rational Recovery, and Save our Selves (SOS) (McKay & Hiller-Sturmhofel, 2011).

Individual psychotherapy is another treatment option available for AUDs. Cognitive behavioral therapy (CBT) is a short-term treatment that addresses dysfunctional relationships between emotions, thoughts, and actions to develop their thoughts and beliefs in more realistic and adaptive ways (Beck, 2011). Patients are provided psychoeducation and develop coping skills to assist them with managing high risk moments for relapse (McKay & Hiller-Sturmhofel, 2011) such as periods of intense craving. Correcting maladaptive belief systems also improves self-efficacy in the patient. CBT is considered an evidence-based approach and is commonly used, however it is resource intensive, requiring the guidance of a psychotherapist.

There are also online treatment options, some of which involve a therapist and some of which are self-administered. A review of self-administered treatment for alcohol and smoking use disorders (Newman, Szkodny, Llera, & Przeworksi, 2011) found that web based interventions can reduce drinking behaviors in those engaged in heavy drinking, even after three months (Cunningham, Humphreys, Kypri, & van Mierlo, 2006; Koski-Jannes, Cunningham, Tolonen, & Bothas, 2007). Interactive web-based problem drinking interventions have also shown reduced alcohol consumption when compared to reading online psychoeducation on alcohol use brochures after six months (Riper et al.,

2008). However, a brief web-based personalized intervention for college drinking led to less drinking after six weeks, but not after six months, when compared to reviewing printed drinking psychoeducation material (Kypri et al., 2004). Web-based interventions for alcohol continue to be studied and developed. Considerations for target population and follow-up length need to be included in future work.

Alcohol dependence severity, a measure of symptoms that indicate physiological or psychological dependence as a result of their alcohol use, has often been used to guide treatment recommendations (Sobell & Sobell, 1995). British surveys (Robertson & Heather, 1982; Rosenberg et al., 1992) found that clinicians included moderation or abstinence as a treatment goal. When a person has a high level of alcohol dependence severity, a patient is typically encouraged to abstain from alcohol. When a patient has a low alcohol dependence severity rating, they are often offered a moderation approach that allows them to continue to drink, but with harm reduction. Miller and colleagues found that when treatment seekers had low alcohol dependence severity moderation treatment outcomes were more successful (Miller & Baca, 1983; Miller & Joyce, 1979). Other factors have been identified as useful when considering moderation as a treatment approach.

In a survey of US based treatment agencies, Rosenberg & Davis (1994) found that after severity of alcohol dependence, drinking history, previous treatment, criminal behavior, liver function test results, and psychological dependence were key to selecting moderation as a treatment goal. The country in which treatment choice research is done greatly influences approaches to harm reduction or moderate drinking and abstinence treatment models. This is particularly true when comparing single payer systems that are

driven by different philosophies than multiple payer profit driven systems. However, in a survey of US and UK treatment providers who were making treatment recommendations based on written case histories, both groups recommended moderation as a treatment goal for patients with low alcohol dependence severity (Cox et al., 2004). A two-year follow-up study of adult men who were advised to reduce drinking found that those who could control their drinking reported fewer dependence symptoms at intake, including morning drinking, shaking, hallucinations, etc. Those who were advised to stop drinking completely had more symptoms of physical dependence at intake.

Relapse to Excessive Alcohol Use

Despite the presence of efficacious treatments for excessive alcohol use reviewed above, the most likely outcome of any attempt to reduce drinking is a return to former drinking patterns. Alcohol Use Disorder can be characterized as a chronic disease (McKay & Hiller-Sturmhofel, 2011) in which cycles of abstinence followed by relapse occur frequently. An article reviewing relapse prevention suggested relapse is "a setback that occurs during the behavior change process, such that progress toward the initiation or maintenance of a behavior change goal (e.g. abstinence from drug use) is interrupted by a revision to the target behavior" (Hendershot et al., 2011). However, there are various definitions of relapse spanning from a "yes" or "no" treatment outcome to a transitional process (Hendershot et al., 2011).

One study reported that, within recently treated persons with AUD, 64% relapsed within a year, and of those who were abstinent at one year, 34% subsequently relapsed in the next two years (Dennis, Foss, & Scott, 2007). Other estimates of long-term relapse rates ranged from 20 to 80% in individuals treated for alcohol use disorder (Jin et al.,

1998; Moyer & Finney, 2002; Weisner, Matzger, & Kaskutas, 2003). In people treated for AUD for the first time, the relapse rate at the 3-year follow-up was 43.4% and 62.4% in those who did and did not seek help respectively (Moos & Moos, 2006). For those were abstinent at the three-year follow-up, the relapse rate at 16 years was 42.9% and 60.5% in those who did and did not seek help respectively (Moos & Moos, 2006).

Given the aforementioned societal and economic costs of excessive alcohol use and given that the most common outcome of attempts to quit or cut down alcohol use is relapse and a return to former drinking patterns, it could be argued that new treatment approaches are required. To develop new interventions, it is crucial to understand the psychological processes underpinning relapse to alcohol. Recent research has focused on the cognitive processes underlying alcohol use in the hope of identifying cognitive targets for intervention. In particular, the cognitive processes underlying impulsivity and impaired control have been investigated. The next chapter will review this literature.

CHAPTER 2: COGNITION AND ADDICTION

As noted in Chapter 1, much recent research has focused on cognitive processes underlying addiction. In particular, recent research has focused on impulsivity and impaired control, manifest as a failure to avoid drinking or to limit consumption once it has begun. This chapter is organized as follows. First, an introduction to the broad cognition and addiction literature will be provided. Second, a more detailed review of impulsivity and impaired control will be provided. Third, a laboratory model of impaired control (R-CASE) will be described. Last, Ecological Momentary Assessment (EMA) will be introduced as a method that can be used to validate the laboratory model.

It should be noted at the outset that the import of cognitive processes in addiction is apparent in several models of addiction. For example, Koob, the Director of NIAAA, conceptualizes addiction as a chronic relapsing disorder that cycles between phases of drug binge and intoxication, withdrawal from the drug, negative affect, and preoccupation with and anticipation of the drug (Koob & Le Moal, 2008). Two elements of the addiction cycle are impulsive and compulsive behavior. These types of behavior are an outgrowth of the brain's executive control process. Moreover, addiction is characterized by a fundamental dysfunction in executive control as evidenced by impaired decision-making and the inability to stop using the drug despite serious adverse consequences to the individual and those around them. As described in more detail later, Robinson and Berridge's (1993) incentive sensitization theory also emphasizes the importance of cognitive processes, including the role of attention to drug cues (described later). Finally, Dr. Nora Volkow, the current NIDA director, places emphasis on the role

of cognitive processes mediated by the prefrontal cortex (described later) (Goldstein & Volkow, 2002).

DUAL PROCESS MODEL

The dual process model (Kahneman, 2011) provides a useful framework for conceptualizing cognitive processes in addiction. First it posits that the brain has two processing systems, system one and system two. System one keeps a person alive when they are driving in a high traffic area, where they need to avoid many obstacles with little warning. System two allows a person to plan out a week of transportation decisions, including using maps and calendars to plan out trips. System one involved fast, unconscious cognition ("automatic processes"). System two is slow, deliberate, and conscious ("controlled processes" or "executive processed") (Kahneman, 2011).

Dual process models have been applied to many areas including appetitive behaviors (Wiers & Stacy, 2006). Dual process theory describes addiction as a conflict between automatic and controlled processes (Shiffrin & Schneider, 1977; Wiers & Stacy, 2006). A variety of automatic processes, including "attentional bias" and "approach bias" (described later) increase the risk of drinking. Executive processes attempt to inhibit the operation of these automatic processes. The focus of this study is on failure of executive cognitive processes to inhibit drinking.

INCENTIVE SENSITIZATION THEORY

Incentive sensitization theory, conceived by Robinson and Berridge (2008), posits that sensitization to drug cues results in changes in brain circuitry that regulates attribution of incentive salience to stimuli. These brain circuitry changes lead to excessive drug cue salience that can become pathological (i.e. the behaviors involved in

substance addiction) leading to disproportionate wanting (desire) for drugs and drug-related cues (Robinson & Berridge, 1993). In essence, incentive sensitization theory suggests alcohol and drugs hijack the brain's motivational system, such that drug taking can also occur in the absence of pleasure (Fischman & Foltin, 1992).

Berridge (2009) captures the above idea in the following:

> "When attributed to a stimulus representation, incentive salience transforms the mere sensory shape, smell or sound into an attractive and attention-riveting incentive. Once attributed, the incentive percept becomes difficult to avoid noticing, the eyes naturally move toward the incentive, it captures the gaze and becomes motivationally attractive, and the rest of the body may well follow to obtain it. (p. 2)"

The statement above indicates that excessive attribution of incentive salience has at least two effects. First, drug users will preferentially attend to drug cues. An "attentional bias" to drug cues occurs when a person orients to, and sustains attention on, drug-related cues more than neutral cues (Field & Cox, 2008). Second, drug users may also automatically approach (move towards) drug cues (Berridge, 2009). An "approach bias" refers to the tendency to automatically approach drug-related stimuli more than neutral stimuli (Wiers at al., 2011).

ATTENTIONAL BIAS

As noted above, attentional bias is the tendency of a person to orient and focus on alcohol or drug related cues (Field & Cox, 2008). Alcohol cues can be varied in type, intensity, and frequency. Cues could include the sound of a typical bar (e.g. glasses clanking), hearing alcohol advertising jingles, or seeing the shape of a bottle that

resembles wine or beer containers Cues can also include words or phrases to include typically benign words such as “thirsty,” or, “bubbles,” or alcohol-related phrases such as, “on the rocks.” While experiencing these cues can lead to craving, craving may also lead to further attentional bias (Franken, 2003). Franken’s model suggests relapse occurs in part due to craving and attentional bias to salient substance cues.

STROOP EFFECT

The addiction Stroop task is a popular method of examining attentional bias that measures cognitive disinhibition (Stevens et al., 2014). It was adapted from the classic Stroop task that originated through many lines of research from 1886-1935, but was first published in English in 1935 by J.R. Stroop and was re-published later in 1992 (MacLeod, 1991; Stroop, 1992). The classic Stroop task has been validated and adapted in hundreds of studies across many areas of focus (MacLeod, 1991) and was first modified for addiction related populations for a smoking task (Gross, Jarvik, & Rosenblatt, 1993).

The Stroop task asks the participant to identify the color of font (blue, green, or red) of a given word by pressing a key on a computer or a button on a hand-held device. Initially, the words are written out colors (blue, green, or red) and the font color is congruent with the written word. Later, the written word is incongruent with the font color. We are using a modified alcohol Stroop task that has been modeled elsewhere and started in 2002 (Cox, Fadardi, & Pothos, 2006; Field & Cox, 2008; Lusher, Chandler, & Ball, 2004; Ryan, 2002). As described in the studies listed above, in this modified version of the Stroop, neutral words are matched in length and complexity to alcohol words. Reaction time, measured in ms, is used as an indicator of attentional bias to the type of

cues presented. We can subtract the reaction time to identify the colors of the neutral words from the reaction time to identify the colors of alcohol words to achieve a score of cognitive interference (Cox, Fadardi, & Pothos, 2006; Field & Cox, 2008; Lusher, Chandler, & Ball, 2004; Ryan, 2002). Slower responding on the alcohol words than neutral words indicates attentional bias and is called the alcohol Stroop effect (Cox, Fadardi, & Pothos, 2006; Field & Cox, 2008; Lusher, Chandler, & Ball, 2004; Ryan, 2002). The Stroop effect can be reliably captured using computers and can be measured several times per day in the participant's natural environment using mobile devices (Szeto, 2017). Pertinent studies that have used the Alcohol Stroop Task in high-risk drinkers are summarized in Szeto, 2017.

DEVELOPMENTAL PERSPECTIVES OF ALCOHOL USE AND ADDICTION

Research has explored how drinking throughout the lifespan influences the development of substance use disorders (Koob & Volkow, 2016). There is a call to develop mental health and substance misuse treatments tailored to the individual patient, including their stage of development, as many adolescents are treated with the same medications and therapy as adults (Lee et al., 2014). Particular attention is being paid to substance use before adulthood (Koob & Volkow, 2016) as drug and alcohol exposure in adolescence is linked to a greater risk of developing a substance use disorder compared to exposure later in life (Grant, Stinson, & Hartford, 2001; Hingson, Heeren, & Winter, 2006; King & Chassin, 2007; Spear, 2013).

Relatedly, adolescent substance use is associated with intensive and chronic use, which may be related to an adolescent brain's attenuated response to aversive stimuli and consequences (Spear, 2013). Incomplete brain development in adolescents has particular

salience when considering cognitive processes that underlie decision-making in drinking, particularly incomplete frontal lobe myelination and synaptic pruning that are essential to executive functioning (Spear, 2013). Further, incomplete executive function development is implicated in risk-taking, novelty-seeking, and peer pressure sensitivity, and all three are characteristic of typical adolescent behavior such as risky drug and drinking (Spear, 2013).

Under conditions of increase emotion and arousal, such as acute stress, an adolescent brain may have attenuated prefrontal cortex activity (Liston, McEwen, & Casey, 2009). Moreover, significant alcohol use in adolescence is associated with impairments in memory, attention, and visuospatial processing (Hanson et al., 2011; Squeglia et al., 2009). Alcohol use in adolescence is also associated with brain changes found in adults with AUD including volume decrease in gray matter regions (Pfefferbaum et al., 1992) as well as increases in white matter volume (Ruiz et al., 2013; both cited in Squeglia et al., 2015). It is not known what downstream effects these developmental changes as result of substance use have on a growing brain, but it is known that as brain regions develop, so do top-down control systems, which help manage emotion and reward driven bottom-up systems (Casey, Getz, & Galva, 2008 as cited in Spear, 2013; Bechara, 2005; Johnstone, 2007). The concepts of top-down and bottom-up systems are key to understanding implications for impulsivity and impaired control and are likely underlying factors that lead to problematic drinking.

BRAIN MECHANISMS UNDERLYING IMPAIRED CONTROL

Cognitive processes underlying impulsivity/impaired control as well as sensation seeking appear to be risk factors for binge drinking, while drinking may reinforce these

underlying processes. Koob's model of addiction has three stages: incentive salience and habit formation form stage one ("incentive salience"), deficits in reward as well as excessive stress form stage two ("negative emotional states"), and executive function comprise is the third stage ("executive function") (Koob & Volkow, 2016). Three neurobiological circuits are key: basal ganglia, extended amygdala, and prefrontal cortex (Koob & Volkow, 2016). Volkow's work focuses on the role of deficits in executive function, particularly in the prefrontal cortex. Koob and Volkow describe these latter deficits as resulting from insula and prefrontal cortex afferent projection dysregulation to the extended amygdala and basal ganglia (Koob & Volkow, 2016). When neurobiological circuits involved in executive function are out of balance there are significant effects including difficulty with inhibitory control and decision-making (Koob & Volkow, 2016). Currently, it is not known whether basal ganglia mediated goal-directed actions and habits or inhibitory deficiencies in the prefrontal regions of the brain are responsible for compulsive responding (Koob & Volkow, 2016).

There is evidence that executive control is key to incentive salience; a study of rats found that dopamine cells suspected to be involved in incentive salience are activated by glutamatergic projections sent by the prefrontal cortex to the ventral tegmental area followed by dopamine projections to the basal ganglia (Geisler & Wise, 2008 as cited in Koob & Volkow, 2016). Studies of brain lesions of the insula and ventromedial prefrontal cortex suggests these areas are key to moral and emotional decision-making (Clark et al., 2008; Verdejo-Garcia et al., 2014; as cited in Koob & Volkow, 2016). The nervous system can be thought of as having Stop and Go systems. The Stop system may control incentive value of decisions and negative affective responses and the Go system,

via the basal ganglia, may be responsible for craving and habit engagement as well as stress (Bechara, Damasio, Damasio, Lee, 1999; Damasio, 1996; Jasinska et al., 2014; Johnstone et al., 2007; Koob & Volkow, 2016; Niendam et al., 2012). Stop and Go systems are especially important when examining impulsive and compulsive behavior.

IMPULSIVITY, COMPULSIVITY, AND PROBLEM ALCOHOL USE

Impulsivity has been described as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others" (Moeller et al., 2001). Moeller approached impulsivity using a biopsychosocial model to explain the role of impulsivity in mental illness. It has also been characterized as swift action without forethought (Hinsie & Campbell, 1970) or as making up one's mind quickly with risk taking and lack of planning (Eysenck & Eysenck, 1977). Moeller also suggests impulsivity may have risk-taking behavior, but not of the type often related to sensation seeking. Leeman's definition of impulsivity, "[being] compelled to drink even if negative consequences are possible because of the rewarding effects [of alcohol]," includes consideration of the role of rewards (Leeman et al., 2014a).

Impulsivity is increasingly being characterized in a neuropsychological framework as a lack of cognitive control (Stevens et al., 2014). In this view, impulsivity is an imbalance of top-down frontal cortex cognitive control and striatal and limbic system (i.e. amygdala) driven bottom-up drives (Bechara, 2005). Impulsivity is characterized by several neurocognitive categories (see Figure 4 from Stevens et al., 2014). Impulsivity can be described as either impulsive action or impulsive choice.

Impulsive action is comprised of motor or cognitive disinhibition. Impulsive choice is broken into delay discounting or impulsive decision-making.

Sher & Trull (1994), Congdon & Canli (2005), and Verdejo-Garcia, Lawrence, & Clark (2008) have all reviewed the relationship between impulsivity and problem alcohol use. Dick et al. (2010) point out that it remains to be seen whether impulsivity is a risk factor for problem drinking or whether impulsivity reflects the same predisposition for alcohol problems. Alcohol use has been found to trigger impulsive behaviors. For example, Goldstein & Volkow (2002) found that the orbitofrontal cortex and anterior cingulate gyrus, both regions connected to the limbic structures, are activated during the drug use cycle of intoxication, craving, and bingeing. Further, they found these same structures play key roles in higher order functions such as inhibiting responses. Relatedly, other findings have demonstrated that impulsivity is implicated in developing alcohol use, alcohol problems, and alcohol disorders (Lejuez et al., 2010). Jentsch & Taylor (1999) reviewed neurocognitive data and suggest that inhibitory deficits (e.g. impulsivity) and enhancements found in learning from conditioned and stimulus-reward reinforcement are the result of repeated drug consumption.

Moeller contrasts impulsivity with compulsivity, which involves planning before the behavior (Moeller et al., 2001). Compulsive behavior may be created by a combination of impairments in control and augmentation in conditioned reward responses to alcohol use (Jentsch & Taylor, 1999). More specifically, habits are a manifestation of compulsion that are triggered by stimuli found in the environment as a result of conditioned responses to drug cues, positive reinforcement, or loss of negative reinforcement such as craving or withdrawal (Stahl, 2013).

As impulsivity and compulsivity have a clear relationship, comparing and contrasting the two is helpful when examining their roles in impaired control. Impulsivity and compulsivity are behavioral symptoms that are linked to brain circuits and are key endophenotypes of substance use disorders (Stahl, 2013). Both are signs the brain cannot stop a behavior with impulsivity as difficulty stopping the initiation of action and compulsivity as difficulty terminating action (Stahl, 2013). Both demonstrate cognitive inflexibility and are conceptualized as bottom-up processes (Stahl, 2013). Impulsivity is generated from the ventral striatum, while compulsivity is generated from the dorsal striatum (Stahl, 2013). Both are mediated by top-down cortical mechanisms and both are impacted by the reward conditioning effects within the amygdala and memory within the hippocampus (Stahl, 2013). Impulsivity and compulsivity occur when there is an imbalance between the top-down and bottom-up systems (Stahl, 2013; see Figure 5).

One theory posits that over time, with mediation from prefrontal cortex, an impulsive action can become compulsive (Stahl, 2013). In this theory, this is how drug or alcohol addiction occurs; a person loses control over their impulsive substance use and their use becomes compulsive (Stahl, 2013). The individual continues compulsive drug use to relieve symptoms of withdrawal (Stahl, 2013).

Using the framework of the NIH's Research Domain Criteria (RDoC; Insel et al., 2010) addiction related domains such as positive and negative valence, social processes, cognition, and regulation of arousal can be examined to better understand how impulsivity and compulsivity function and interact to promote unwanted substance use behavior (Brooks et al., 2017). Among these questions are whether impulsivity is a state or trait, what the role of compulsivity is in relapse, and whether impulsivity and

compulsivity act sequentially, concomitantly, antagonistically, complementarily, or some combination (Brooks, 2017). Koob & Volkow (2016) suggest impulsivity precedes compulsivity in addiction, however more evidence in line with RDoC criteria may help examine and measure compulsivity and impulsivity (also cited in Brooks et al., 2017).

MEASURING IMPULSIVITY

Impulsivity is now often viewed as biologically based and heritable (Lejuez et al., 2010). Biological studies have examined potential indicators of impulsive behavior such as cerebrospinal fluid serotonin metabolite levels (which are higher in those who enact planned aggressive or violent actions) (Linnoila et al., 1983). Several behavioral tasks have also been developed to examine impulsivity in the laboratory across three neurocognitive areas (also see Fig. 3): 1) choice-reward paradigms where preference for a small immediate reward over a delayed large reward is impulsive, 2) punishment/extinction paradigms, and 3) attention/response disinhibition paradigms where impulsive responses are made prematurely (Moeller et al., 2001).

Among the choice-reward type tasks, the Delay Discounting Task (DD) is used in several forms including experiential (Reynolds & Schiffbauer, 2004) and question based (Richards, Zhang, Mitchell, and De Wit, 1999). The Delay Discounting Task is based on a random adjustment algorithm to create estimates of discount (Richards et al., 1999). It has been used to demonstrate impulsivity as a predictor of alcohol self-administration in rats (Poulos, Le & Parker, 1995) and as part of neuroimaging protocols examining impulsivity in the context of alcohol use, including by the NIAAA laboratory associated with the CASE task (Bjork, Momenan, & Hommer, 2009).

The Wisconsin Card Sorting Test (WCST) (Heaton, 1981) is an example of the punishment/extinction category of paradigms that involves shifting sets or rules. The participant is instructed to match cards, but the rules of each set are not articulated. Feedback on whether the matching is correct or incorrect guides the participant as they use abstract reasoning and flexible problem solving to successfully complete the tasks (Heaton, 1981). The WCST has been used in studies that assess for the effects of intoxication on perseveration (Lyvers & Maltzman, 1991) and in studies of how prenatal alcohol exposure affects executive functioning (Connor et al., 2000).

The differential reinforcement of low-rate responding schedule (DRL) is a paradigm that has been used to assess impulsivity in populations that are both suicidal and substance misusing (Dougherty et al., 2004) and is often used in evaluating drug effects (Kirshenbaum et al., 2008). In DRL, a minimum time to withhold a response is established before earning a reinforcement, making it a response-inhibition task (Kirshenbaum et al., 2008). Responses that occur prematurely are not reinforced and are coded as impulsive responses. Once questions are asked in DRL paradigms, they cannot be used again as participants are able to discern the contingencies (Dougherty et al., 2004).

The Balloon Analogue Risk Task (BART) is a laboratory based computer task that measures and rewards risky behavior until a point when further risk results in worse outcomes (Lejuez et al., 2002). Essentially, the participant increases the size of a balloon, earning money with each increase, while simultaneously increasing the risk that the balloon will burst and all money gained will be lost (Lejuez et al., 2002). The BART task

has been used to study impulsivity and risk-taking in substance misusers and adolescents (Carroll et al., 2011; Lejuez et al., 2003).

Questionnaires are also used to gather self-report impulsivity data. The Eysenck Impulsiveness Questionnaire (Eysenck et al., 1985) and the Barratt Impulsiveness Scale (Patton & Stanford, 1995) are both widely used in research and provide the opportunity to learn about various behaviors patterns. However, these measures cannot be repeatedly administered, as would be the case in sets of EMA data.

IMPAIRED CONTROL

An important aspect of alcohol addiction is the inability to limit drinking, either through abstaining or following the onset of drinking. Impaired control has been defined as "a breakdown of an intention to limit consumption" (Heather, Tebbutt, Mattick, & Zamir, 1993; See summary of studies in Table 1). DSM-IV and DSM-5 both include behaviors linked to impaired control in characterizing alcohol use disorders, "[alcohol] is often taken in larger amounts or over a longer period than was intended" and "there is a persistent desire or unsuccessful efforts to cut down or control [alcohol] use" (American Psychiatric Association, 2000; 2013). Despite being included as part of the composite symptom set for both DSM-IV and DSM-5 diagnosis of alcohol use disorders, psychometric data suggest impaired control is an independent construct (Heather et al., 1993; Kahler et al., 1995; Read et al., 2006; Leeman et al., 2012). Leeman et al., 2014a (citing Heather, 1995; Heather at al., 1993) discuss impaired control as a continuum of severity which may parallel the shift in severity from impulsivity to compulsivity in addictions (Everitt et al., 2008).

Impaired control over drinking is an early sign of problem drinking (Leeman, Patock-Peckham, & Potenza, 2012). Alcohol can be consumed at high rates over extended periods of time as ethanol has a low toxicity rate, which makes drinking alcohol highly dangerous for those with impaired control (Knapp, Ciraulo, & Kranzler, 2008). Impaired control is especially important to study as it could be used to identify drinkers at risk of developing alcohol use disorders (Leeman et al., 2012).

Questionnaire measures of impaired control, such as the Impaired Control Scale (ICS), have been shown to predict drinking in the field (Heather, 1993; Leeman et al., 2012) as well as laboratory models of alcohol self-administration (Leeman et al., 2014b; Wardell et al., 2015). In order to examine alcohol self-administration along with the negative consequences of drinking, Leeman et al. (2013) included a payment reduction component to discourage excessive alcohol use in a bar-based three-hour self-administration of beer. When participants drank excessively, their performance on several cognitive-motor tasks worsened, and consequently participants lost money. Further, participants were given drinking guidelines before self-administration to discourage excessive alcohol use during their self-administration period. The authors found that those who had received both the drinking guidelines and the proportional payment reduction interventions drank at a slower pace and consumed more non-alcoholic drinks. However, the experimental group had a broad range of drinking and some did drink to excess (Leeman et al., 2013). As impaired control appears to have a great influence over excessive alcohol consumption, there is a pressing need to develop further treatment interventions that target impaired control in alcohol consumption.

ALCOHOL PRIMING

Alcohol priming can play a key role in impaired control and potential relapse in substance and alcohol use disorders (Leeman et al., 2014a). A number of observations indicate that a priming dose of a drug can increase drug use motivation and use. First, in animal models, low doses of drugs reinstate responding after extinction (Leeman et al., 2014a). Thus, a low dose of drugs appears to motivate animals to self-administer drugs (Leeman et al., 2014a). Second, human drug users who use a small amount of their drug of choice report increased subjective desire for more and possible continued re-use of the substance (de Wit, 1996). Third clinical experience indicates that one drink may lead to another and that a single drink can precipitate relapse. Alcohol priming will be manipulated in the current study, as described later.

Although small doses of alcohol may increase risk of relapse in many heavy drinkers, controlled drinking has been a treatment goal for some mild-to-moderate problem drinkers (Marlatt et al., 1993). Research on whether controlled drinking is a viable treatment goal for heavier drinkers has used a priming dose of alcohol to simulate real world drinking. Dawe and colleagues (2002) devised a study of highly dependent drinkers who underwent a cue exposure paradigm that included a priming dose of alcohol in comparison to the behavioral self-control training (Miller et al., 1992; Miller & Munoz, 1982). Behavioral self-control training focuses on developing: specific goal setting, consumption and urge to drink self-monitoring, developing strategies to limit or avoid drinking, reinforcing achievement of goals, identifying situations with high-risk of drinking, and developing coping strategies.

The cue exposure paradigm was used for the goal of reducing alcohol cue reactivity, including the consumption of alcohol. 61 men (mean age 41.8 years) were exposed to alcohol cues (sight, taste, smell of their preferred drink) and raised blood alcohol level through alcohol consumption in a controlled environment (Dawe et al., 2002). Participants were systematically exposed to drinking cues with return to baseline desire to drink in between each stage. The first stage was exposure to the sight of their drink, then to the touch of the glass or can, then to the smell, and finally exposure to the taste. Participants were then reminded of the treatment rationale (to resist the urge to drink), but were allowed to continue to drink. Positive and negative urge to drink was measured every four minutes and a subjective desire to drink rating sheet was completed approximately every ten minutes. Breath alcohol concentration ratings were also recorded, especially before the session was complete. A drinking log was also kept by participants in order to track field drinking outcomes (Dawe et al., 2002). The authors found no difference between the two treatments, but both groups had lower consumption than at the start.

Two other randomized trials have been completed with similar methodology (Heather et al., 2000; Sitharthan et al., 1997). The study by Heather and colleagues (2000) also found no difference between treatments (priming dose vs. cognitive behavioral treatment), but both groups of participants had reductions in drinking. In Sitharthan et al.'s study (1997), priming exposure and cognitive behavioral therapy conditions were administered to 52 participants in groups of 3-4 people over six weekly 90 minute sessions. At six-month follow-up, cue exposure participants reported significantly fewer drinking occasions and fewer drinks overall.

LABORATORY MODELS OF IMPAIRED CONTROL

Although, as noted above, impaired control can be assessed using questionnaires, to better understand the psychological processes underlying impaired control Ramchandani and colleagues have developed a novel human laboratory model that assesses actual consumption behavior indicative of impaired control. This impaired control model is based on prior self-administration models (Ramchandani et al., 2011), and serves as the laboratory model for the present study. This model uses intravenous (IV) alcohol self-administration (IV-ASA) combined with a physiological-model-based algorithm that provides exquisite control of alcohol exposure while assessing alcohol consumption behavior and its determinants (Zimmermann et al., 2013). The paradigm has been used in several studies of the pharmacokinetics of alcohol (Sato et al., 2001; Ramchandani et al., 2001; Neumark et al., 2004) as well as to examine various determinants of the pharmacodynamics of alcohol (Morzorati et al, 2002; Blekher et al., 2002; Ramchandani et al., 2002; Ramchandani et al., 2006, Gilman et al., 2008; Ramchandani et al., 2011).

The Computer-Assisted Self-infusion of Ethanol (CASE) method, also known as Computerized Alcohol Infusion System (CAIS), extends the model-based algorithm by providing participants flexibility in choosing when to push a button to receive a "drink" via an alcohol infusion, while providing the investigator with wide flexibility in controlling the subsequent time course of breath (and therefore brain) alcohol exposure (Stangl et al., 2016). The CASE paradigm has demonstrated high test-retest reliability and has been used to examine determinants of alcohol-seeking and self-administration or consumption behavior, including medication effects (Plawecki et al., 2013), genetic

variation (Suchankova et al., 2015), family history of alcoholism (Zimmermann et al., 2009), and drinking history (Stangl et al., 2016).

The CASE method involves continuous interactions with research and clinical staff and may include speaking with the principal investigator. While these staff members are not readily visible during the CASE self-administration or button-press portion of the paradigm, they are present in the room separated from the participant by a curtain. The participant is also aware that their self-administration behavior is being monitored. These elements of the protocol are especially important as they can be influenced by demand characteristics. Relatedly, social desirability, or socially desirable responding, could have an influence on self-administration or response to self-report measures. Several scales of social desirability have been used in studies of drinking (Perinelli & Gremigni, 2016) and could be incorporated into future studies, with thoughtful consideration of how the information could be used to improve study design. To date, no studies have examined the role of demand characteristics or social desirability on alcohol self-administration. The current study contributes to understand differences between lab and EMA data collection on drinking and self-administration behavior.

EMA takes place without the presence of research or clinical staff. Although the participant's drinking behavior is being measured, EMA data is collected without the context of a research setting. It is reasonable to expect that data collected via EMA will be less susceptible to demand characteristics. However, because data collected via EMA is gathered in the participant's natural environment, it is possible that participants are more likely to be influenced by peer suggestibility. Affiliating with peers who drink has a strong influence on alcohol use (Hawkins at al., 1992; Jacob & Leonard, 1994), which

may be due to high levels of affiliation among drinkers with similar patterns of use (e.g. binge drinking) (Osgood et al., 2013). The tendency to drink more when surrounded by peers who drink more has even been demonstrated in lab settings using heavy drinking confederates (Larsen et al., 2009). Investigating differences between lab and field measures of drinking is an important step in understanding the role of impaired control in binge drinking.

Most relevant to the current proposal, Ramchandani and colleagues recently developed a novel variation of the CASE model (Resist CASE, or R-CASE) where participants are offered money to resist self-administering alcohol. Their ability to withhold self-administration is an index of their ability to exert control over self-administration. This ability-to-resist has been modeled for nicotine in cigarette smokers (McKee et al., 2009), and has been used to examine determinants of smoking relapse (McKee et al., 2012), and treatment outcomes in smoking cessation (McKee et al., 2015). There has been limited research on human laboratory models of impaired control over alcohol consumption, indicating a critical need to examine this. However, for R-CASE to be useful, it needs to be validated against drinking behavior in the real world. This is the focus of this dissertation.

ECOLOGICAL MOMENTARY ASSESSMENT (EMA)

Ecological momentary assessment (EMA) is a method of investigating the behavior, mood, thoughts, and feelings of participants while they are in their natural environment. EMA can be also be used to study cognitive processes (Shiffman, Paty, Gyns, Kassel, & Hickcox, 1996; Waters & Li, 2008; Waters, Marhe, & Franken, 2012; Waters, Miller, & Li, 2010). Assessing people in the field increases the validity of the

assessments and allows for assessment the moment an event occurs. EMA also allows for highly detailed assessment of a person's current functioning and provides data sufficient to observe longitudinal patterns or brief changes (Epstein et al., 2009; Waters et al., 2004). For example, if a person initiates an assessment when they are experiencing craving, EMA responses can be used to characterize the state of the person as they face an increased risk of relapse.

EMA methodology has been described in terms such as daily diary or experience sampling methods (Onnela & Rauch, 2016). However, EMA has specific associations with leveraging technological developments and is currently administered through smartphones, often using an app. Smartphones are equipped with software or a mobile application that allows a participant to initiate assessments or respond to a beep that notifies the participant to complete an assessment, which are referred to as random assessments (RAs). As a result of advances in digital data gathering, researchers can monitor real time compliance (Stone et al., 2003). Compliance in EMA can be monitored closely (Stone et al., 2003). In our study, monitoring will be real-time as data will be sent immediately courtesy of data plans provided by cell phone providers. Prior studies using RAs to assess high risk drinkers have compliance rates that tend to be greater than 70% (See Szeto, 2017) and a recent meta-analysis of EMA in substance users found a pooled compliance rate of 75.06% (Jones et al., 2018).

EMA has been used to scrutinize the psychological processes underlying drinking behavior (Morgenstern, Kuerbis, & Muench, 2014). EMA involves assessing phenomena at the moment they occur in a person's natural environment, usually using mobile devices. Assessments may be done at random times ("random assessments"; RAs) to

capture naturally occurring behaviors. Data from EMA studies are detailed and can reveal longitudinal patterns of change within a few hours (e.g., Epstein et al., 2009; Shiffman & Waters, 2004), and have examined drinking (Huntley et al., 2015). EMA has also been used in alcohol studies to assess alcohol interventions (Mitchell et al., 2012; Witkiewitz et al., 2014). EMA has also been used to assess predictors of self-reported excessive drinking in heavy drinkers (Collins et al., 1998).

Research has demonstrated that participants follow study instructions when using mobile phones to complete EMA assessments and that reports of alcohol use when the drinking event occurs is valid when compared to method of paper and pencil self-monitoring, which is typical in research (Collins, Kashdan, & Gollnisch, 2003). While paper and pencil self-monitoring has been validated when compared to biochemical indices (Sanchez-Craig & Annis, 1982), it is subject to poor compliance and a lack of reliable information about the day/time of when assessments were completed (Collins, Kashdan, & Gollnisch, 2003). With the increase of technology use, mobile or smart phones provide opportunity for more frequent and reliable data gathering in the field. Pertinent studies that use EMA to investigate high-risk drinking are summarized in Szeto, 2017 and the EMA questions for the dissertation are in Figure 6.

COMPARING LAB AND FIELD MEASURES

A crucial question is the extent to which a laboratory model of impaired control (R-CASE) actually predicts alcohol consumption in the field. Notably, for other addiction-related measures, laboratory assessments may not always be strongly related to real-world behavior. Pertinent studies are summarized in Table 2.

For example, following a laboratory CR assessment, laboratory CR measures were not accurate predictors of smokers' craving or reactions to cues assessed during 3 weeks of EMA in the real world (Shiffman et al., 2015). In a study of adolescent drinkers, Ramirez and Miranda (2014) examined whether alcohol CR elicits craving under controlled and natural conditions and if craving could then predict alcohol consumption. They found a main effect of alcohol cues on craving and that craving that took place in the laboratory predicted the likelihood and intensity of alcohol craving in the natural environment. Elevated daily craving levels in the field also predicted alcohol consumption in the field. Finally, Litt et al. (2000)'s study of 26 men undergoing inpatient or outpatient alcohol treatment at a VA hospital found that laboratory based CR urge to drink ratings correlated modestly with field urge to drink and drinking frequency. There are sparse data on studies that compare laboratory and field based data and what is currently available, which focuses on craving, has mixed findings. More research in this area in needed and the proposed study can help develop this literature base.

SUMMARY

Recent studies in addiction have examined cognitive process in addiction in the hope of identifying cognitive targets for intervention. Both automatic processes (such as attentional bias) and controlled processes (such as cognitive control and impulsivity) have been investigated. This study focuses on the breakdown of control (impaired control) that occurs in some drinkers. A laboratory model of impaired control (R-CASE) has been described that may yield new insights into this phenomenon. First, R-CASE needs to be validated against data in the field. The study uses Ecological Momentary

Assessment (EMA) to validate the laboratory model. Our study is described in the following chapter.

CHAPTER 3: STUDY RATIONALE, PRELIMINARY DATA, AND SPECIFIC AIMS

STUDY RATIONALE

Excessive alcohol use remains a significant public health problem in the US. A better understanding of the psychological processes underlying excessive drinking is needed so that more effective interventions can be developed. Recent research has focused on impaired control, defined as a failure to avoid drinking or to limit consumption once it has begun (Leeman et al., 2014a). Questionnaire measures of impaired control (e.g., Impaired Control Scale, ICS) have been shown to predict drinking behavior (Heather et al., 1993).

To better understand the processes underlying impaired control, as described in Chapter 2 we developed a novel human laboratory model (R-CASE) that assesses actual consumption behavior indicative of impaired control. If R-CASE is a good model, it could be used to evaluate whether impaired control can be modified by psychological or pharmacological manipulations and could be a valuable tool to study reduced-risk drinking interventions in clinical populations. But first, this laboratory model (R-CASE), as well as the parent laboratory model (CASE), need to be validated against actual drinking behavior in the field. Figure 1 provides an overall timeline for both the parent and dissertation studies, while Figure 2 focuses solely on the dissertation study. Figure 3 illustrates the conceptual model of the specific aims.

PRELIMINARY DATA

A recent study by Ramchandani and colleagues characterized the relationship between impulsivity, impaired control of alcohol consumption, and CASE in non-dependent drinkers (Vaughan et al., 2019). Participants (n=152) completed a CASE

session where they could push a button to receive individually standardized alcohol infusions. Subjective response was assessed using the Drug Effects Questionnaire (DEQ). Drinking history was assessed using 90-day timeline followback (TLFB) assessment. Impulsivity measures included Barrett's Impulsivity Scale (BIS), UPPS-P Impulsive Behavior Scale, and the rate constant from the Delayed Discounting (DD) task. A subset (n=48) completed the Impaired Control Scale (ICS), which assessed control over drinking.

Impulsivity and ICS measures were positively associated with TLFB. Individuals with higher ICS scores also had higher impulsivity scores. Those with higher impulsivity also had greater alcohol self-administration, and higher perceptions of liking and wanting more alcohol. Individuals with higher ICS scores also had greater alcohol self-administration, and higher subjective perceptions of liking and wanting more alcohol. Those who achieved binge-level BrACs during the CASE session had heavier drinking histories, greater DD, lack of premeditation, and greater attempts to control their drinking in the past. There were strong associations between CASE, subjective response, and multiple measures of impulsivity and impaired control, suggesting that these traits may be important factors in understanding alcohol-seeking behavior in a non-dependent population. Mediation analyses indicated that impaired control was a significant mediator of the relationship between impulsivity and alcohol consumption (Vaughan et al., 2019). The data indicate the utility of human laboratory paradigms like CASE in unraveling relationships between measures of control and alcohol consumption behavior.

Research involving similar types of participants has been conducted within the NIAAA intramural program. A human laboratory study of heavy non-treatment seeking

drinkers that combined CASE with functional magnetic resonance imaging to examine the effects of intravenous ghrelin on alcohol self-administration and brain function recruited from a similar population using similar recruitment procedures (Farokhnia et al., 2017). Among key demographic variables for the 11 CASE procedure participants, the average age was 39.86 (*SD*=3.54) years, 8 identified as male, 9 identified as African American, and average education was 13.36 (*SD*=0.49) years. A second recent intramural study from NIAAA that examined drug effects on heavy drinkers using CASE and functional magnetic resonance imaging recruited from a similar population using similar recruitment procedures (Vatsalya et al., 2015). Of the 29 participants who were included in the analyses separated into two conditions, 12 placebo and 17 drug treatment, respectively the average age was 37.9 (*SD*=13.5) years and 29.8 (*SD*=9.4) years, and 11 and 14 identified as male. Given the similarities across both studies and the current study in targeting heavy drinkers and using similar recruitment tools, we expected similar demographic variables in our study.

In our study, we are investigating the role of impaired control of alcohol consumption in community-based binge drinkers in the greater Washington, D.C. metropolitan area recruited using advertisements seeking healthy and drug-free non-treatment seeking alcohol drinkers who are between 21-45 years of age. Despite the non-random nature of our sample, we anticipate our results will generalize to heavy drinkers who both do and do not experience impaired control episodes and are generally at a higher risk of mortality (Smyth et al., 2015). Note that due to the demands of using iPhones to complete the study, there may be a recruitment bias and limited generalizability to those who are comfortable using smartphones on a regular basis.

FIELD

Our USUHS laboratory, the Laboratory of Cognitive Interventions (LOCI) collaborated on an EMA study in alcohol-dependent outpatients (N=43) (reported in Szeto, 2017). Participants carried a mobile device in the field for 4 weeks and completed 2020 EMA assessments. Compliance was adequate (Szeto et al., 2019, in press).

Also, pertinent to the proposed study, LOCI has conducted EMA studies permitting comparison of data derived from lab and field assessments. In a smoking cessation study, lab measures of a self-report assessment (craving) and a cognitive assessment (implicit attitudes) were correlated with EMA assessments (rs = .67 & .54 respectively, ps < 0.001).

Most pertinent to the current study, Sells and colleagues conducted a pilot study in which participants completed both the R-CASE laboratory measure and two or three weeks of EMA. (These data are included as part of the dissertation and are not yet published). Most relevant to the current study, there was considerable variability in motivation to abstain and drinking both between individuals and within individuals.

SPECIFIC AIMS

Heavy drinkers (N=16) were scheduled to complete a CASE (free access) session and up to two R-CASE sessions (As noted earlier, 4 participants completed R-CASE in two separate sessions, one with a priming alcohol exposure and one without). Participants completed up to six weeks of EMA to assess motivation and drinking. The overall goal was to examine the validity of the laboratory models. The specific aims were:

Specific Aim 1: To examine the association between alcohol self-administration in the lab during the free access session (Lab Consumption) and drinking behavior in the real-world, assessed using EMA.

Hypothesis 1.1: Individuals who self-administer more alcohol in the lab during the free access session will report more drinking in the real world.

Hypothesis 1.2: The effect of Lab Consumption on real-world drinking should be moderated by motivation in that the effect should be stronger when participants are motivated to drink normally.

Specific Aim 2: To examine predictors of resisting and drinking in the lab and field

Hypothesis 2.1: Individuals with higher levels of impaired control, as assessed by a self-report assessment, will be less able to resist drinking in the lab and field.

Hypothesis 2.2: Individuals with higher levels of impulsivity, as assessed by self-report and cognitive assessments, will be less able to resist drinking in the lab and field.

Exploratory Aim 1: To examine the association between ability to resist alcohol self-administration in the lab (Resist) and the ability to abstain from drinking in the real-world, assessed using EMA.

Exploratory Hypothesis 1.1: Individuals who are better able to resist drinking in the lab are better able to abstain from drinking (report less drinking) in the real world.

Exploratory Hypothesis 1.2: The effect of Resist on drinking should be moderated by drinking motivation in that the effect should be stronger when participants report that they are motivated to abstain.

Exploratory Aim 2: To examine within-subject predictors of drinking in the field assessed using EMA

Exploratory Hypothesis 2.1: Craving, assessed using EMA, will be prospectively associated with drinking, assessed using EMA

Exploratory Hypothesis 2.2: Negative affect, assessed using EMA, will be prospectively associated with drinking, assessed using EMA

Hypothesis 2.3: Drinking goal, and motivation to cut-down/abstain from drinking, assessed using EMA, will be prospectively associated with drinking, assessed using EMA

Laboratory and EMA data from this study may ultimately help to 1) develop algorithms that can predict when an individual is at risk of drinking, and 2) develop interventions, administered in the field, to reduce the risk of poor outcomes associated with drinking. See Figure 3 for a conceptual overview of the dissertation study.

CHAPTER 4: METHODS

PRE-PILOT WORK

Twelve participants with usable data completed the pre-pilot portion of the study. While the pre-pilot (first 12 subjects) shares many familiarities with data from subsequent subjects (4 subjects), there are notable differences worth examining as the pre-pilot work informed the parameters for the subsequent 4 subjects (see Table 3).

Participants were recruited for both heavy and binge drinking (meeting criteria of 15+ for women and 22+ for men drinks per week in addition to one binge drinking day per week). Participants in the pre-pilot study underwent a screening session, two laboratory sessions (a free access baseline CASE session and an RCASE session), and one follow-up session with a brief intervention. Participants also completed two to four weeks of the EMA component of the study. For the RCASE sessions, participants were only provided with a prime session (the subsequent 4 participants also had an additional no-prime session). Quantity of monetary reinforcers varied during the pre-pilot phase of the study as we sought to calibrate to the most effective amount that would allow participants to consider delaying self-infusion for 50% of the delay phase.

Other differences include the addition of a requirement that pilot participants (last 4 participants) stay overnight in the NIAAA clinical center for observation after each laboratory self-administration session, whether they drank or not. This was due to safety concerns, but also to eliminate the unintended incentive to leave the study session earlier if the participant did not self-infuse during a self-administration session.

Finally, to increase compliance with completing random assessments, during the pilot phase of the study, participants were informed the would be paid $3 for a random assessment and only $1 for a self-initiated make-up session. They were also informed at

the end of each EMA entry that they would receive an additional $5 for keeping their phone charged throughout the study. The total payment for the four visits was $700 (compared to $980 for the pilot phase of the study), and neither figure includes the monetary reinforcer reward or the EMA payments.

PARTICIPANTS

Overall, sixteen male and female heavy drinkers between 21-45 years of age and in good health were recruited from the Washington D.C. area. A broad age range was used as the patterns of heavy drinking that we are seeking can take years of drinking to develop. Participants were recruited through the NIH Normal Volunteer Office, by word of mouth, using a novel video, and through local advertisement (newspapers, flyers, newsletters, websites) approved under a screening and assessment protocol (see Appendix A). Given that heavy drinking does not have a universally agreed upon definition and the criteria used to define heavy drinking vary from study to study, it is important to incorporate both amount of alcohol consumed per occasion and amount of alcohol consumed per week as both dimensions of use are relevant in assessing risk related to excessive alcohol consumption (Rehm et al., 2012). Therefore, we selected heavy drinkers using a definition that takes into account both pattern of drinking and total consumption. For pattern of drinking, we required participants to have on average at least one binge drinking day per week, using the NIAAA definition of 5 or more drinks for men and 4 or more drinks for women (NIAAA website, n.d., *Drinking levels defined*). For total consumption, we used an average of 15 or more drinks per week for women and 22 or more drinks per week for men as this level of drinking has been shown to confer increased risk of mortality (Smyth et al., 2015).

Inclusion criteria: Male participants must have consumed an average of 22 or more standard drinks per week and females must have consumed an average of 15 or more standard drinks per week during the past 90 days. Participants must have on average at least 1 binge drinking day per week during the last 90 days, defined as a day in which 4 or more standard drinks were consumed for females and 5 or more standard drinks were consumed for males. Participants must be able and willing to refrain from consuming alcohol 24 hours prior to each alcohol self-administration session.

Exclusion criteria include current or prior history of serious medical illness, positive hepatitis or HIV test at screening, clinically significant liver function laboratory tests, current history of psychiatric illness other than alcohol use disorder, current diagnosis of substance use disorder other than alcohol use disorder, and a positive result on urine drug screen or breathalyzer test. For females, pregnancy, intention to become pregnant, or breastfeeding; all female participants will undergo a urine beta-hCG test to ensure that they are not pregnant prior to study. Use of prescription or over-the-counter medications (such as anti-histamines, pain medications, anti-inflammatories) known to interact with alcohol within 2 weeks of the study, medications known to inhibit or induce enzymes that metabolize alcohol (such as anti-fungals) within 4 weeks of the study. Current or prior history of alcohol-induced flushing reactions.

PROCEDURES:

Laboratory Visit 1: Screening and Baseline Measures. After provision of verbal informed consent participants were screened according to the protocol including: medical history, drinking history, family history of alcoholism, Structured Clinical Interview for DSM psychiatric diagnoses including alcohol and substance use disorder,

physical examination, blood tests for routine blood chemistry, liver enzymes, hepatitis and HIV screen, urine screen for illicit drugs, the NEO-PI personality inventory, and an Alcohol Flushing Questionnaire.

Laboratory Visits 2-4. Participants attended three self-administration sessions approximately one week apart in the NIH Clinical Center. Participants were asked about their alcohol consumption habits. They also completed a number of self-report measures of impaired control and other measures.

Alcohol self-administration. During Visit 2, participants underwent a baseline CASE session (without Resist) in order to acclimatize to the effects of IV alcohol and obtain a baseline measure of lab consumption of alcohol. This session is also referred to as the "free access" visit. Visits 3 and 4 were Resist CASE sessions with and without an alcohol prime in a counter-balanced order (for the last 4 subjects; the first 12 subjects only received the primed RCASE) (see Table 4 and Figure 1).

Resist CASE: During Visits 3 and 4, participants arrived at the Clinical Center in the morning after abstaining from alcohol for 24 hours. The participant was seated in a comfortable chair in a patient room in the unit, out of sight of the infusion pumps and instructed in the procedures and limits for electing infusions in the paradigm. At experimental time 0, a directed priming interval of approximately 25 mins was initiated. The participant was prompted to press a button to initiate four consecutive exposures 2.5 min apart (at time = 0, 2.5, 5, 7.5 (10, 12.5) min). This resulted in a peak BrAC of approximately 30 mg% at 10 min (or 45 mg% at 15 min). During the next 20 mins, the alcohol button remained inactive so participants could experience the result of their initial button presses. Following this priming interval, the subject began the delay phase in

which they were asked to resist subsequent infusions (time varied depending on which stage of the pilot completed, ranging from 50 to 120 minutes). For every 5 minutes they did not press the button they earned a monetary reward (ranging from $0.01-$10.00 and starting at $2.00). The incremental reward amount was determined based on pilot work that lead to 25-75% delay in pressing for alcohol during the delay phase (McKee et al., 2012). As soon as the subject self-administered alcohol, the delay phase ended and the participant began an ad libitum open-bar administration lasting 1.5 hours. During this phase, subjects had free access to push the self-infusion button for a standardized exposure of IV alcohol, except when the CASE system predicted that an additional button press would result in a peak BrAC above 120 mg%, which is the upper limit for BrACs achieved in this study. When this occurred, the push button was inactivated, with the subject's knowledge, until the time when the predicted peak BrAC was below the upper limit. The procedure for the no prime Resist CASE session was identical to that described above except that the subjects did not receive any alcohol infusions during the priming interval.

Smartphone training. A staff member trained participants on how to use the smartphone and provided the smartphone and charger to be used during six weeks of EMA starting during Visit 2.

Laboratory Visits 5-7. Three laboratory visits served as follow-up visits. Participants were asked about their alcohol consumption habits. They also completed a number of self-report measures (Table 5 and Figures 6, 7, and 8).

EMA Assessments between each weekly laboratory visit. Participants completed up to four randomly timed smartphone field assessments per day. Participants

were instructed to complete a participant-initiated assessment (a “make-up” assessment) when they failed to complete an RA. Participants were able to delay a random assessment for up to 20 minutes when they were unable to complete it right away.

Brief Intervention: At Visit 7, participants were debriefed about the study and were provided a brief motivation based intervention for their heavy drinking behavior. The intervention followed the clinical guidelines for treatment of alcohol use disorders as described in the NIAAA publication "Helping patients who drink too much: A clinician's guide."

MEASURES

Laboratory Session Alcohol Measures

The Drug Effects Questionnaire (DEQ), the Alcohol Urge Questionnaire (AUQ), the Biphasic Alcohol Effects Scale (BAES) are self-report measures of alcohol effects including feelings of high, intoxication, urge, stimulation and sedation. The Subjective Units of Distress Scale (SUDS) measures self-reported feelings of stress, and part 3 of the Impaired Control Scale (ICS) (see Figure 8) assesses perceived control. A mood questionnaire that used analogous items to the five mood questions asked during the EMA assessment (adapted from Epstein et al., 2009) was administered (see Figure 7). The CASE Experience Questionnaire (CEQ), which assesses the monetary value of the IV alcohol infusion and the standard alcohol drink correlate of their IV alcohol exposure, was administered.

EMA MEASURES

At each assessment, which was prompted by a recurring beep, participants completed a set of measures that assessed drinking and smoking, craving for alcohol,

craving for tobacco, perceived control over alcohol use, motivation to reduce drinking, mood, stress, fatigue, and hangover. Alcohol abstinence motivation was assessed with the items: "How motivated are you to cut down on your drinking for the next 24 hours?" (1=Not at all; 2=A little; 3=Moderately; 4=Quite a bit; 5=Extremely), and "How motivated are you to completely avoid drinking for the next 24 hours?" (1=Not at all; 2=A little; 3=Moderately; 4=Quite a bit; 5=Extremely). Drinking Goal was assessed with the following item: "At the current time would you rather maintain your normal drinking pattern, cut down on your drinking, or avoid drinking altogether?" (Response Options: "Maintain normal drinking pattern"; "Cut down on drinking"; "Avoid drinking altogether"). For the drinking question, participants indicated how many glasses of alcohol they consumed since the previous assessment (1=no drinks; 2=1-2 glasses; 3=3-4 glasses; 4=5-6 glasses; 5=7 or more glasses); this item was used in our previous alcohol EMA study (preliminary studies and Figure 6).

A classic Stroop task as well as a modified alcohol Stroop task that assess cognitive control and attention to alcohol cues was assessed during EMA, consistent with previous protocols conducted by LOCI. Classic and alcohol Stroop tasks were selected at random from a list of 24 tasks (12 classic Stroop tasks, and 12 alcohol Stroop tasks). Both versions began with a practice session to assist the participant with orienting to the task and both versions had buttons on the screen indicating "BLUE", "RED", and "GREEN" that were presented in a different order for each assessment to avoid practice effects.

The classic Stroop Task was used to assess cognitive disinhibition, a subcomponent of impulsive action (Stevens et. al, 2014). Individuals were presented neutral words or color incongruent words (e.g., "RED" in blue ink) and instructed to

identify the color of the word as quickly as possible, while ignoring the meaning of the word. The classic Stroop task permits examination of whether poor cognitive inhibition predicts more drinking, both between-subjects and within-subjects. These data complement laboratory data on impulsivity collected in this study. The classic Stroop task included the following practice session with stimuli presented in varying order per assessment: VVVVVVVV, IIIIIIII, QQQ, PPPP, YYYYYY, DDDD, UUU, MMMMM, JJJJJ, HHHH, XXXX, TTTTTT, LLLLL, AAAAA, NNNNN, WWWW, FFF, ZZZZ, CCCC, LLLLLLLLL, KKKKKKKK, SSSSSSSS, EEEE, OOOO. The classic Stroop task then presented the color words in varying order, and the order varied for each assessment.

The modified Alcohol Stroop Task was used to assess cognitive processes involving attentional bias to alcohol cues (Cox et. al, 2006). Individuals were presented alcohol-related words (e.g., alcohol, drink) or neutral words (e.g., cliff, air) and instructed to identify the color of each word as quickly as possible, while ignoring the meaning of the word. The alcohol Stroop task permits examination of whether poor attentional bias predicts more drinking, both between subjects and within-subjects. The modified alcohol Stroop task included a set of neutral words with similar length and complexity as the set of alcohol related words. Words were selected to be relevant to current era and region. Each set was presented in varying orders across sets and across order of presentation within assessments. The neutral words were as follows: WINDS, AIR, CLIFF, HIGHLAND, COUNTRY, TUNNEL, BRIDGE, VALLEY. The alcohol words were as follows: DRINK, BAR, LIQUOR, TAVERN, BOTTLE, BOOZE, ALCOHOL, COCKTAIL.

Compensation

Participants received $700 or $980 for the study (pre-pilot and pilot phases respectively), in addition to money earned during the CASE sessions. To promote compliance, participants received $3 for each RA that they completed and $1 for each self-initiated assessment. Similar contingencies have yielded adequate compliance in previous studies (Kerst & Waters, 2014 and Szeto, 2017).

Analytic Plan

Linear Mixed Models (LMMs) were used for the primary analyses (Kreft & de Leeuw, 1998). SAS PROC MIXED was used for continuous outcomes assumed to be normally distributed in the population (conditional on model covariates), and SAS PROC GLIMMIX was used for other types of outcome. LMMs handles the fact that assessments are nested within participants, and that participants have different numbers of assessments. Each LMM used a random intercept, and a covariance structure of (SP_POW) for the residuals within subjects to account for unequal time intervals (described in more detail below). Multiple linear regressions were used to analyze the relationship between different variables stemming exclusively from lab data.

All models included Day of study (continuous variable) and Gender. Bolger and Laurenceau (2013) recommend including a measure of time in EMA analyses, and Gender is typically included as a covariate in analyses involving alcohol consumption. Age was also considered as a covariate. Age was not associated with lab consumption at the "free access" visit (p=.36) or with lab consumption at the primed RCASE visit (p=.59). Moreover, inclusion of age in models did not substantially change the conclusions of primary analyses. Therefore, age was not included as a covariate in the primary analyses.

EMA drinking (1-5) (reported drinking since the last assessment) was treated as a continuous variable in primary analyses; supplementary analyses, described below, also tested models using different assumptions concerning the distribution of the EMA consumption measure. Decomposition of multilevel interactions followed the approach outlined by Preacher et al. (2016); for example, level 1 time-varying EMA covariates (e.g., Motivation) have both between and within components requiring separation. To illustrate any significant interactions, simple slopes would have been constructed using the methods of Aiken and West (1991) (this was not necessary following the results of these analyses). All tests used $\alpha = 0.05$ and were 2-tailed. For all models, the parameter estimate was provided as an (unstandardized) measure of effect size.

Hypothesis 1.1 states that individuals who self-administer more alcohol in the lab during the "free access" session report more drinking in the real world.

To analyze Hypothesis 1.1, Lab Consumption (continuous) at the "free access" visit was the IV and Drinking during EMA was the DV.

Hypothesis 1.2 states that the effect of Lab Consumption on real-world drinking should be moderated by motivation in that the effect should be stronger when participants are motivated to drink normally.

To analyze Hypothesis 1.2, Lab Consumption (continuous) at the "free access" visit was an IV, Motivation during EMA was a second IV, and the interaction between Lab Consumption and Motivation was a third IV. Drinking during EMA was the DV. As noted above, the interaction was decomposed following the guidance of Preacher et al. (2016). This procedure is described in more detail in the results section.

For the Motivation measure we used a "binary" motivation measure derived from the two 5-point Motivation scales. Recall that these two measures were: How motivated are you to cut down on your drinking for the next 24 hours?" (1=Not at all; 2=A little; 3=Moderately; 4=Quite a bit; 5=Extremely), and "How motivated are you to completely avoid drinking for the next 24 hours?" (1=Not at all; 2=A little; 3=Moderately; 4=Quite a bit; 5=Extremely). The binary motivation item was coded as 0 ("Not at all" responses to both Motivation items) or 1 (any other responses). Thus the coding of 1 indicates the presence of *any* motivation to cut down or avoid drinking over the next 24 hours.

Hypothesis 2.1 states that individuals with higher levels of impaired control, as assessed by self-report and cognitive assessments, will be less able to resist drinking/consumption in the lab and field. To analyze Hypothesis 2.1, the predictor variables included the Perceived Control scale. The lab DV was the total alcohol consumed in session 2 (the resist session) and the field DV was EMA consumption quantity. (Multiple regression analyses were used for these analyses, as gender was included as a covariate.)

Hypothesis 2.2 states that individuals with higher levels of impulsivity, as assessed by self-report and cognitive assessments, will be less able to resist drinking in the lab and field. To analyze Hypothesis 2.2, the predictor variables included BIS and Delayed Discounting. The lab DV was the total alcohol consumed in session 2 (the resist session) and the field DV was EMA consumption.

Power Analyses

Analyses were conducted using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) and assume alpha = 0.05 and a 2-tailed test. Estimates account for the correlated

nature of repeated measures data, as indexed by the intraclass correlation coefficient (ICC). The "effective sample size" was computed using the total number of study assessments divided by the VIF (Variance Inflation Factor) (VIF = 1+((average number of observations per person) -1)*ICC); here the ICC is the intraclass correlation coefficient for the DV. For Hypothesis 1.1, we had assumed 37 participants, 6 weeks of EMA, 75% compliance, and ICC = .5; the "effective sample size" was 73.4, and there would have been power = .82 to detect an effect size rho = .32 (i.e., a medium effect size), between Lab Consumption (level 2) and EMA drinking (level 1). If ICC = .3 (i.e., EMA data are less correlated), the effective sample size = 121.1, and power = .80 to detect rho = .25 (small-to-medium effect size). Power to detect associations between lab measures (e.g., in Specific Aim 2) will be lower due to the smaller number of observations.

Covariance Structure

Continuous outcomes analyses conducted with SAS and SPSS used "type=SP_Power" for the covariance structure. This specification improves upon previous reliance on type=AR(1) R-sided covariance structure (R matrix), which researchers have argued assumes equal time intervals between assessments. When gathering daily diary data (as used by Hoeppner et al., 2008), this equal time interval is true, but it is not quite true for EMA data at the assessment-level (Schwartz & Stone, 2007). Schwartz and Stone (2007) have created alternative code (in SAS) to apply to data with unequal intervals (a detailed description of the methodology can be found in Schwartz and Stone p. 88-89) called modified first order autoregression. They argued that it might provide an optimal fit for mixed models with unequal time intervals. We elected to use the SP_Power covariance structure as it accounts for unequal time intervals

between assessments and because it was possible to replicate findings across software packages (SPSS and SAS). (The code used by Schwartz and Stone does not appear to be available in SPSS.)

Supplementary Analyses

Due to our measurement scale of the dependent variable, there are concerns that the normality assumption of the linear mixed models would not be met. We completed supplementary analyses using negative binomial regression to check if results were robust using those methods. As noted later, some models failed to converge (or experienced other problems) using these methods, and in these cases a model using a Poisson distribution was used instead.

Exploratory Analyses

To further understand the variables measured in this study, we conducted exploratory analyses using LMM and the same covariates as above (gender and day) with IVs Lab Resist in Proportion of Minutes (from the primed RCASE session) and EMA Alcohol Consumption as the DV. As with Hypothesis 1.2 we also examined motivation to abstain (coded as the binary variable) as a moderator variable

We also examined the prospective relationships between the IVs Alcohol Craving, Negative Affect, Drinking Goal, Motivation 1 (to cut down on drinking), and Motivation 2 (to stop drinking) on the DV next EMA Alcohol Consumption using LMM and Gender and Day as covariates. The IVs were constructed by calculating the mean of all assessments aggregated by subject and subtracting the mean from each individual variable measured, this resulted in a *Deviation* score. The *Deviation* score assessed the within-subject association in multilevel data (Bolger and Laurenceau, 2013). For example

a significant association between *Deviation* Craving and Alcohol Consumption before the next assessment would indicate that when participants report more craving than their person-specific average they drink more before the next assessment. The DV was constructed using the Lead function in SPSS, which allows for the next EMA assessment to be the prospective outcome of the prior EMA IV.

CHAPTER 5: RESULTS

Overall, 12 participants were enrolled in the first phase of the study and four were enrolled in the second phase of the study making a total of 16 participants across the entire study. Fifteen participants completed one baseline CASE ("free access") session, 13 completed a primed RCASE session, and 4 completed an unprimed RCASE session. The study ranged from one week to five weeks with one to three lab infusion visits. As noted in Table 6, participants were predominantly male, White, in their mid-thirties, with low income, and at least a high school education. In the 90 days prior to the study, participants reported drinking approximately 6 drinks per drinking day, drinking 66 out of 90 days, with a total of 375 drinks.

Descriptive Statistics

Descriptive statistics for field and laboratory data are reported in Tables 10 and 11, respectively.

EMA Data

Of the 16 participants, four completed the entire study. All participants completed at least one EMA assessment, contributing a total of 954 EMA assessments. Of the 954 EMA assessments, 440 assessments (from five participants) included either a Classic Stroop task (n=220 assessments) or a Drug Stroop assessment (n=220 assessments, see Table 7).

Participants completed 77.64% of the expected number of assessments (4 assessments per day for the duration of the study). For the 15 subjects for whom data were available, 52.18% of completed assessments were random assessments, and 48.82% were make-up assessments. (Data on type of assessment was not available for the first

participant due to loss of data). Of the assessments, 28.68% were completed in the morning (before noon), 30.88% were completed between noon and 6.00 PM, and 40.44% were completed in the evening (between 6.00 PM and midnight).

Across all 954 assessments, participants reported that their drinking goal was to maintain normal drinking 61.43% of the time, with the remaining 38.57% of assessments indicating a desire to cut down (24.11%) or avoid drinking altogether (14.47%). Across all assessments, average level of craving was 1.58 (*SD*=0.50) (1-5 scale; 1= no craving), average responses on "feeling stressed" was 1.57 (*SD*=0.37) (1-5 scale, 1 = no stress), average "feeling tired" was 1.65 (*SD*=0.38) (1-5 scale, 1 = not tired), and average "feeling hungover" was 1.19 (*SD*=0.25) (1-5 scale, 1 = not hungover). Anger, sadness, and anxiety (measures of Negative Affect) were all assessed with binary scales. Participants reported feeling not angry, not sad, and not anxious on 72.01% of assessments. They endorsed feeling one symptom of negative affect (either anger, sadness, or anxiety) on 17.71% of assessments, two symptoms of negative affect on 7.34% of assessments, and all three symptoms of negative affect on 2.94% of assessments. Participants reported average levels of cigarettes smoked since the previous assessment of 1.23 (*SD*=0.48) (1-5 scale, 1=no cigarettes smoked since the last assessment). On the craving for cigarettes item, participants reported an average craving of 1.14 (*SD*=0.20) (1-5 scale, where 1 indicates no cigarette craving).

Variability in Drinking Goal and Motivation

The intraclass correlation correlation coefficients (ICCs) for Drinking Goal, Motivation to Cut Down, and Motivation to Avoid Drinking were .38, .48, and .43, indicating substantial between-subject variability in these measures. The ICCs also indicate that a substantial amount of variability is within-subjects (.62, .52, and .57 for Drinking Goal, Motivation to Cut Down, and

Motivation to Avoid Drinking respectively). Another method to index within-subject variability of each measure is the within-subject *SD* (as calculated for the EMA drinking item earlier). The average within-subject *SD* for Drinking Goal was 0.47 (*SD* = 0.29). The average within-subject SD for Motivation to Cut Down, and Motivation to Avoid Drinking were 0.80 (*SD* = 0.45) and 0.80 (*SD* = 0.49) respectively. Given the significant within-subject associations reported in the dissertation, it may be useful in future analyses to treat Drinking Goal, Motivation to Cut Down, and Motivation to Avoid Drinking as dependent variables, to try to determine the predictors of change in these variables.

Reliability and Validity of "EMA Drinking"

The following findings support the reliability and validity of the EMA Drinking measure (1-5 scale) used in the dissertation study. First, using an intercept-only model, LMM revealed that intercepts for subjects significantly differ using mixed models ($p < 0.05$), indicating that there are between-subject differences in subjects' "true" mean drinking scores. Second, although not using a multilevel framework, one can estimate the internal reliability of subject-level EMA Drinking using a split-half approach. The split-half correlation between EMA drinking on "even" & "odd" days is 0.78 (using the Spearman-Brown correction), suggesting that subject mean scores on the EMA Drinking measure have reasonable internal reliability. Third, for assessments occurring on the same day, reported drinking at the later assessment was strongly associated with the interval (number of hours) since the previous assessment, *PE* = 0.06, *SE* = 0.016, $p < 0.001$. This is expected because participants have more opportunity to drink during longer intervals. Fourth, using LMM, there was no evidence for a main effect of Day, *PE* = -0.008, *SE* = 0.006, $p = 0.16$. In other words, there was no evidence that reported drinking declined over time; the absence of a decline is expected, because participants are not treatment-seeking. Fifth, consistent with past literature (e.g., Black et al., 2018), an LMM revealed that participants reported more drinking reported at "Weekends" (Friday, Saturday, Sunday) vs. "Weekdays" (Monday, Tuesday, Wednesday, Thursday), *PE* = 0.38, *SE* = 0.13, $p = 0.01$. Last, as reported in exploratory analyses,

there was a significant within-subject association between Deviation Craving and Drinking before the next assessment.

Lab Data

In terms of lab measures, 15 participants completed the "free access" session, thereby providing data on the CASE measure. (One participant withdrew from the study prior to completing this session). Thirteen participants completed the primed RCASE session, and four participants completed the unprimed RCASE session.

Participants who completed the primed RCASE session were designated as having resisted drinking if they did not drink during the session. If the participant did drink, they did not resist. Of the 13 participants who completed the primed RCASE session, 5 resisted (see Table 8). Those who did not resist self-administered alcohol on average 62% of the way through their primed RCASE session. Overall during the primed RCASE session, participants drank 16.27 (*SD*=11.96) grams of alcohol and achieved a peak breath alcohol measure of 45.69 (*SD*=42.82) mg%.

Total alcohol consumed varied across the three lab infusion sessions, with the greatest consumption taking place during the free access visit (visit 1) at 59.54 (*SD*=31.05) grams of ethanol (see summary in Table 8). Peak breath alcohol during the free access session was 91.22 (*SD*=43.00) mg% over 18.13 (*SD*=6.81) infusions received (also known as button presses). During the free access infusion session, participants reported craving (AUQ) scores of 20.73 (*SD*=11.26) at baseline and craving (AUQ) scores of 28.00 (*SD*=8.87) at peak level.

At session 1, across the 15 participants total ethanol consumed, peak breath alcohol level, and total button presses to administer ethanol were all strongly correlated (all *ps* <.0001). The correlation between total ethanol consumed and peak breath alcohol

level was $r = .92$, the correlation between total ethanol consumed and total button presses was $r = .88$, and the correlation between peak breath alcohol level and total button presses was $r = .85$.

During the second self-infusion (RCASE) session, which included the alcohol prime condition, as noted above, 5 participants resisted drinking for the entire duration. For those that delayed drinking, they delayed, on average, for 62% of the time allotted to free access of ethanol infusions.

At session 2, the correlation between total ethanol consumed and peak breath alcohol level was $r = .52$ ($p = 0.07$), the correlation between total ethanol consumed and total button presses was $r = .57$ ($p = 0.04$), and the correlation between peak breath alcohol level and total button presses was $r = .98$ ($p < 0.0001$).

Specific Aim 1

Hypothesis 1.1 tested whether individuals who self-administer more alcohol in the free access session report more drinking in the real world measured using EMA. Table 9 (see also Figure 9) reveals that there is no evidence in support of the hypothesis of a relationship between Total EtOH and EMA alcohol consumption.

Hypothesis 1.2 tested whether the association between lab consumption from the first self-infusion session and real world drinking using EMA is moderated by motivation in that the association should be stronger when participants are motivated to drink normally. Table 9 (see also Figure 10) reveals that there is no evidence in support of the hypothesis of moderation by motivation of a relationship between Total EtOH and EMA alcohol consumption.

Following Preacher et al. (2016), one can decompose the Total EtOH x Motivation interaction into two components, a Total EtOH x *Mean* Motivation interaction and a Total EtOH x *Deviation* Motivation interaction. The Total EtOH x *Mean* Motivation interaction tests whether the association between Total EtOH and EMA alcohol consumption is stronger in individuals with generally higher level so Motivation (in Preacher et al.'s terminology, a 2 x (2 → 1) interaction). The Total EtOH x *Mean* Motivation interaction was not significant (*PE* = -0.015, *SE* = 0.008, $p = 0.09$). The Total EtOH x *Deviation* Motivation interaction tests whether the association between Total EtOH and EMA alcohol consumption is when individuals repot higher level of Motivation than their person-specific average in Preacher et al.'s terminology, a 2 x (1 → 1) interaction. The Total EtOH x *Deviation* Motivation interaction was also not significant (*PE* = 0.0006, *SE* = 0.004, $p = 0.88$). In sum, across multiple analyses, there was no evidence that the association between lab alcohol consumption and EMA alcohol consumption was moderated by motivation.

Specific Aim 2

Hypothesis 2.1 examined whether individuals with higher levels of self-reported impaired control were less able to resist drinking in the lab during session 2 (primed RCASE) and in the field as measured by EMA. Table 10 reveals there is no evidence in support of the hypothesis of a linear relationship between lab perceived control and lab consumption of ETOH during session 2. Table 10 also reveals there is no evidence in support of the hypothesis of a relationship between lab perceived control and EMA alcohol consumption. In sum there was no evidence for an association between the lab measure of perceived control and alcohol consumption in the lab or field.

Hypothesis 2.2 examined whether individuals with higher levels of self-reported impulsivity will be less able to resist drinking in the lab during session 2 and in the field as measured by EMA. Table 10 (see also Figure 11) reveals that impulsivity and lab consumption were (unexpectedly) negatively correlated (as impulsivity goes up, drinking goes down). Note that a multiple regression analysis using Proportion of Time Resisted (rather than Total Alcohol Consumption) as the dependent variable (and impulsivity and gender as independent variables), did not yield a significant association for impulsivity, $PE = 0.024$, $SE = 0.013$, p - .09 (not reported in Table 10). A lab measure of delayed discounting was not associated with lab consumption. Table 10 also reveals there was no evidence in support of the hypothesis for a relationship between impulsivity and EMA alcohol consumption. Similarly, there was no evidence for a relationship between delayed discounting and EMA alcohol consumption.

Supplementary Analyses

The supplementary analyses were conducted to ascertain if the results of linear mixed model analyses held under different assumptions. Initially, a negative binomial model was used (using SAS PROC GLIMMIX, dist=negbin). If the negative binomial model failed to converge (or the final Hessian matrix was not positive definite) then a Poisson distribution was assumed (dist=p). In select cases, the models assumed an ordinal dependent variable (dist=multi); these models also yielded similar conclusions (results not reported). Briefly, the conclusions did not differ when using these models under different distributional assumptions. Details for all analyses, including Specific Aim 2, Hypothesis 2.1 and Hypothesis 2.2 are reported below.

Negative Binomial Regressions

Hypothesis 1.1 tested whether individuals who self-administer more alcohol in the free access session report more drinking in the real world measured using EMA. Table 9 reveals there is no evidence in support of the hypothesis of a relationship between total ETOH consumed during the free access visit and EMA alcohol consumption. Hypothesis 1.2 tested whether the effect of lab consumption from the first self-infusion session on real world drinking using EMA should be moderated by motivation in that the effect should be stronger when participants are motivated to drink normally. Table 9 reveals there is no evidence in support of the hypothesis of moderation by motivation of a relationship between total EtOH consumed during the free access visit and EMA alcohol consumption.

Hypothesis 2.1 examined whether individuals with higher levels of self-reported impaired control will be less able to resist drinking in the lab during session 2 and in the field as measured by EMA. Table 10 reveals that when using a Poisson model there was no evidence for an association between lab perceived control and drinking, $PE = 0.013$, $SE = 0.008$, $p = .14$. Hypothesis 2.2 examined whether individuals with higher levels of self-reported impulsivity will be less able to resist drinking in the lab during session 2 and in the field as measured by EMA. Table 10 reveals that when using a Poisson model there was no evidence for an association between lab perceived control and drinking, $PE = 0.006$, $SE = 0.006$, $p = .29$.

Exploratory Analyses

Resisting in the Lab and Field

Exploratory Aim 1, Exploratory Hypothesis 1.1 examined whether individuals who were better able to resist drinking in the lab during session 2 were better able to

abstain from drinking (reported less drinking) in the real world as measured using EMA. Table 11 reveals there is no evidence in support of a relationship between proportion of time resisting in the lab and EMA alcohol consumption.

Exploratory Aim 1, Exploratory Hypothesis 1.2 examined whether the effect of resisting alcohol on drinking before the next assessment was moderated by drinking motivation such that an association should be stronger when participants report that they are motivated to abstain. Table 11 reveals there was no evidence in support of the association between resisting in the lab and EMA alcohol consumption (before the next assessment) was moderated by motivation to abstain (see also Figure 12).

As for analyses for Specific Aim 1, following Preacher et al. (2016), one can decompose the Proportion of Time Resisting x Motivation interaction into two components, a Proportion of Time Resisting x *Mean* Motivation interaction and a Proportion of Time Resisting x *Deviation* Motivation interaction. The Proportion of Time Resisting x *Mean* Motivation interaction tests whether the association between Proportion of Time Resisting and EMA alcohol consumption is stronger in individuals with generally higher level of Motivation (in Preacher et al.'s terminology, a 2 x (2 → 1) interaction). The Proportion of Time Resisting x *Mean* Motivation interaction was not significant (*PE* = 0.90, *SE* = 0.59, $p = .17$). The Proportion of Time Resisting x *Deviation* Motivation interaction tests whether the association between Proportion of Time Resisting and EMA alcohol consumption is greater when individuals reported higher level of Motivation than their person-specific average (in Preacher et al.'s terminology, a 2 x (1 → 1) interaction). The model testing the Proportion of Time Resisting x *Deviation* Motivation interaction failed to converge.

Prospective Within-Subject Associations in EMA Data

A series of analyses examined within-subject associations in the EMA. In all cases, the primary predictor variables were *Deviation* scores.

Exploratory Aim 2, Exploratory Hypothesis 2.1 tested whether EMA assessed craving was prospectively associated with EMA assessed drinking. Table 12 reveals that as EMA alcohol craving increased, alcohol consumption assessed before the next assessment increased by .209 units, F (1, 2066.05) = 7.36, p =0.007.

Exploratory Aim 2, Exploratory Hypothesis 2.2 tested whether EMA assessed negative affect was prospectively associated with EMA assessed drinking. Table 12 reveals there is no evidence in support of a relationship between EMA negative affect and the next EMA alcohol consumption response.

Exploratory Aim 2, Exploratory Hypothesis 2.3 tested whether EMA assessed drinking goal was prospectively associated with EMA assessed drinking. Table 12 reveals that as EMA drinking goal increased (to cut down or stop drinking), alcohol consumption assessed in the next EMA response decreased by 0.23 units, F (1, 115.659) = 5.38, p =0.022.

Three additional Exploratory Aim 2 analyses were completed. The first tested whether EMA assessed *Deviation* motivation to cut down on drinking (question labeled Motivation 1) was prospectively associated with EMA assessed drinking. Table 12 reveals no evidence in support of the hypothesis of a relationship between EMA motivation to cut down on drinking and EMA alcohol consumption. The second additional Exploratory Aim 2 analysis tested whether EMA assessed *Deviation* motivation to stop drinking (question labeled Motivation 2) was prospectively associated

with EMA assessed drinking. Table 12 reveals that as EMA motivation to stop drinking increased, alcohol consumption decreased by 0.205 units, F (1,4.567) =10.50, p =0.026. The third tested whether EMA assessed *Deviation* binary motivation to cut down/stop drinking was prospectively associated with EMA assessed drinking. As EMA binary motivation increased, alcohol consumption decreased by 0.205 units, F (1,11.4) =11.4, p =0.007 (not shown in Table 12).

CHAPTER 6: DISCUSSION

The main findings of the study were as follows. First, regarding Specific Aim 1, there was no evidence for an association between total ethanol consumed in the lab and EMA alcohol consumption. There was also no evidence that motivation to cut down or remain abstinent moderates the association between lab and EMA alcohol consumption. Second, regarding Specific Aim 2, - unexpectedly - impulsivity and lab consumption of alcohol during the Resist-CASE visit (with alcohol prime) were negatively correlated. As impulsivity increased, lab consumption decreased. However, no other significant associations were documented in analyses for Specific Aim 2. For example, delayed discounting and lab consumption of alcohol during the Resist-CASE visit (with alcohol prime) were not correlated. Further, there was no evidence for a relationship between perceived control/impulsivity/delayed discounting and EMA alcohol consumption. Regarding the exploratory analyses, there was no evidence that ability to resist drinking in the lab was associated with drinking in the field. However, a number of within-subject predictors of drinking, including motivation to abstain from alcohol use, were identified. All findings are discussed in detail below.

Specific Aim 1: Association Between Lab Self-Administration and EMA Drinking

As noted above, contrary to hypothesis, there was no evidence for a significant association between alcohol self-administration in the lab and EMA drinking behavior. This conclusion was consistent across multiple supplementary analyses using different assumptions. A number of factors may have made it difficult to detect this association, and these factors are reviewed below.

First, the magnitude of the true association between lab and field measures may not be large, meaning that it would be difficult to detect particularly in a study with a small sample size. For example, for other studies using various addiction-related measures, there is not always a strong association between lab and real-world behavior, as summarized in Table 2. In the small literature comparing lab and EMA measures, inducing craving is the typical focus, not drinking behavior. Based on prior findings (Litt et al., 2000; Ramirez & Miranda, 2014; Shiffman et al., 2015), we would expect that the true effect size for an association between a laboratory and field measure is a small to medium effect size. More specifically, Shiffman et al.'s study of 190 daily smokers measuring smoking and drinking in the lab and field using EMA found a range of standardized regression coefficients of -0.04 to 0.18 for the relationships between cue reactivity and EMA craving. In the same study, the standardized regression coefficients of the association between cue reactivity and EMA smoking ranged between 0.01 and 0.26, and the average correlation was 0.03. Ramirez and Miranda (2014) studied cue reactivity and alcohol craving in 42 non-treatment-seeking adolescents in the lab and field using EMA and found an effect size range of 0.01 to 0.40, small to medium effect size. Litt and colleagues (2000) studied predictors of alcohol craving in 26 male patients undergoing VA inpatient or intensive outpatient program treatment for alcohol use disorder. Measures were gathered in the lab and in the field following discharge from treatment. Effect sizes ranged from 0.03 to 0.31, small to medium.

Overall, in terms of our study, previous limited effect sizes suggest that the probability of our detecting an effect between lab and field measures is low. It is possible that we did not find an association between lab consumption and field drinking due to the

low power of our limited sample size. For example, if the true effect size for the association between lab drinking and field drinking is 0.3, then using the same assumptions as in the power analysis presented earlier we would have an estimated power of ~ 0.30 to reject the null hypothesis.

These points notwithstanding, it should be noted that an unpublished study on smoking cessation completed by Waters et al. found that lab measures of self-reported craving and cognitively assessed implicit attitudes had correlations with EMA assessments at r=.67 and .54, respectively (both large effect sizes), suggesting that large effect sizes may be observed in some contexts.

Additionally, the question of reactivity to self-monitoring drinking should be considered. In our study, we did not find a significant effect of Day, meaning that EMA drinking did not decline significantly over time, which might be expected if self-monitoring reactivity were at play. A related study using EMA ("ambulatory assessment"), transdermal sensors, photo, and survey procedures found that participants did not report substantial reactivity (Fairbairn & Cranford, 2016). However, previous research has explored potential complications and more attention should be paid to including measures of reactivity in future EMA studies (Barta, Tennen, & Litt, 2012). Future consideration of including wearables, explored below, may help address reactivity concerns.

To summarize, the most important considerations when interpreting the null associations are 1) the notion that the true effect size may not be large, and 2) the small sample size (in terms of number of subjects) used. Nonetheless, other factors, including self-monitoring reactivity, may serve to reduce the association between the lab and field

drinking measures. Further, measurement, for example, of the EMA drinking variable used may not capture the characteristic captured in the lab drinking measure. The "level 2" analyses reported in this dissertation essentially examine whether the lab measure of consumption is associated with average reported drinking (1-5 scale) since the previous assessment. This analysis may potentially ignore other important information in the EMA drinking data that may relate to the lab drinking measure.

Other potential approaches to analyzing the EMA drinking behavior data that could assess aspects of drinking beyond the current study are considered here. One key area to consider is how to interpret drinking variability in EMA data. For example, it may be useful to code the EMA data in terms of binge episodes, so that it is possible to examine whether lab drinking is associated with number/proportion of binges across the study period. A significant challenge is the lack of clear definition of what constitutes a binge episode beyond number of drinks. As stated earlier, four or more drinks for women and five or more drinks for men in a drinking episode is considered a binge by NIAAA (NIAAA, n.d., *Drinking levels defined)*. However, the period of time that constitutes a binge episode is not clearly defined in the literature. For example, a woman drinking four drinks over six hours, while consuming glasses of water between each drink, will have blood and breath alcohol levels that differs significantly when compared to a woman who consumes four drinks in a one hour span without other liquids. This scenario can be further complicated by other factors that affect alcohol absorption, distribution, and metabolism such as body-weight and ingesting food before or during alcohol consumption. Moreover, during EMA, RAs were spaced throughout the day roughly four

hours apart. As such, an RA may or may not capture an entire drinking episode for the purposes of identifying a binge episode.

The laboratory portion of this protocol is able to take these personalized factors into account however, it is not feasible to match the same drinking circumstances in the field. Considering our simple example of alcohol and water, depending on which binge criteria is used, both women may be considered as having a binge episode. Defining a binge drinking episode becomes even more difficult when considering criteria that includes consequences of drinking as criteria for binge drinking (Wechsler, 1994). Consideration of including a self-initiated assessment at the onset and termination of drinking, with measures that capture amount and time of drinking, may be helpful in future studies that seek to measure binge drinking episodes.

As is common with all laboratory studies, the "atypical" nature of the lab setting could influence subjects in different ways (e.g., some subjects may feel little motivation to self-administer alcohol in a sterile lab setting, others may appreciate the novelty of self-administration in such a setting). These individual differences in responses to the lab setting, this might further reduce the magnitude of lab-field associations, although we are not aware of any data that speaks to the magnitude of this influence is on the lab data.

More generally, an additional note to consider with our CASE and RCASE data is that we may have inadvertently assessed boredom, a desire to end the session early, as well as novelty seeking, particularly in light of the novelty of IV self-administered alcohol, or other unknown factors. While these factors may influence study findings, they are not related to the constructs being assessed (e.g., propensity to binge, failure to resist), but are important to consider in future study designs.

One should also note that the lab measure assesses IV alcohol self-administration whereas the EMA measure assesses oral self-administration. One might wonder how the different administration methods influence the data. It would be useful to examine the association between lab (IV) and lab (oral) administration; to the best of our knowledge these data have not been collected. However, data suggest that oral (lab) and IV administration (lab) do have similar effects on subjective measures ((Plawecki et al., 2019).

It is also important to recognize that some EMA data were distal in time from the CASE assessment. Data suggest that the association between two assessments of lab drinking (in the same participants) demonstrates good test-retest reliability (Stangl et al., 2017), and does not appear to weaken as the duration between assessments becomes longer (up to 4 weeks) (Ramchandani, personal communication, 05/23/19). Nonetheless, in supplementary analyses, it may be useful to examine if associations between lab drinking and EMA drinking become weaker for data more distal from the lab assessment. On a similar theme, it may also be useful to examine the temporal stability of reported drinking solely in the EMA data.

In sum, it is possible to identify a number of factors that can potentially reduce the magnitude of lab-field associations (Specific Aim 1) to include, but not limited to: Different administration methods (IV vs. oral) in two settings; individual differences in responses to lab context (including IV component); EMA coding does not capture the "binge" nature of lab assessment; and much EMA data is "distal" from the free access session. The relative importance of these factors is not yet known, although they could be examined in future studies using larger samples.

Specific Aim 2: Examining Predictors of Drinking in the Lab and Field

As noted earlier, analyses generally revealed non-significant associations between predictor variables and drinking in the lab/field. An exception was that impulsivity and lab consumption of alcohol during the Resist-CASE session were negatively correlated, such that as impulsivity increased, consumption decreased, which was the opposite direction hypothesized in the study. However, it is important to note that these results were only just significant at p=0.046, and the finding would not have been significant if a correction had been applied.

When evaluating the null associations for Specific Aim 2, many of the considerations reviewed for Specific Aim 1 will apply to Specific Aim 2. As explored in the previous section about Specific Aim 1, previous studies by Litt et al.,2000, Ramirez & Miranda, 2014, and Shiffman et al., 2015 indicate small to medium effect sizes when comparing lab and field measures. Note that the sample size for the lab measure from the primed R-CASE session (n=13) was even smaller than the sample size of the CASE session (n=15), which provided the data for Specific Aim 1, meaning that power may have been lower for some analyses relating to Specific Aim 2.

Regarding coding of field data, it may be possible to code EMA data to better capture failure to resist in the field. For example, in larger samples it may be possible to identify the episodes after which participants reported binges in the 24 hours following a response in which they indicated that they intended to avoid drinking for the next 24 hours.

In terms of the lab to lab associations examined for Specific Aim 2, in a study with our same NIAAA collaborators of 48 healthy social drinkers, attempted control, a

subscale from the Impaired Control Scale used in the current study, was correlated with IV alcohol self-administration at r^2 =0.2 (large effect size) and with peak breath alcohol level at r^2 =0.1 (medium effect size) (Vaughan et al., 2019). Note, however, that these data derive from the CASE paradigm (rather than the RCASE paradigm). In addition, a second subscale from the Impaired Control Scale, failed control, was not predictive of IV alcohol administration (Vaughan et al., 2019). Another study from the same group examined 112 healthy social drinkers across IV alcohol administration sessions and found large effect sizes for average breath alcohol levels (r=0.6), peak breath alcohol levels (r=0.7), total number of rewards (r=0.72), and total amount of ethanol consumed (r=0.7) (Stangl et al., 2016). Further, the group found high large effect sizes for exposure measures in session 1 (r=0.88-0.97) and in session 2 (r=0.86-0.97).

Wardell, Le Foll, and Hendershot (2018) studied IV alcohol consumption in 16 heavy episodic drinkers aged 19-22. In considering the correlation between peak breath alcohol difference (actual consumption minus intended consumption from a question administered before the task), the Impaired Control Scale attempted control subscale correlated 0.17, while the failed control subscale correlated 0.36 (small and medium effect sizes, respectively). Overall, in terms of our study, previous limited effect sizes suggest that the probability of our detecting an effect between lab and lab measures is limited, but their magnitude suggests that it may be more likely to detect lab to lab association than to detect a lab to field association.

As noted earlier, impulsivity was negatively correlated with consumption in the RCASE session. These findings run counter to the theoretical background and literature base that suggest that underlying impulsivity, which is an executive dysfunction

characterized by a lack of planning to react to stimuli (Moeller et al., 2001), appears to be a risk factor for binge drinking. Indeed, Leeman has defined impulsivity as "[being] compelled to drink even if negative consequences are possible because of the rewarding effects [of alcohol]" (Leeman et al., 2014a). Future research, preferably using larger sample sizes, could benefit from more extensive collection of impulse related behaviors in screening and during EMA assessments.

Exploratory: Association Between the Ability to Resist Alcohol Self-Administration and Ability to Abstain from Drinking

As noted earlier, there was no evidence in support of the hypothesis of a relationship between lab resisting in minutes and EMA alcohol consumption, nor was there evidence supporting the moderation of an association by motivation to cut back/avoid drinking for the next 24 hours. As with earlier analyses, it is possible that our sample size was too small to detect this relationship. To our knowledge, there is no literature base that relates to our findings. Our data could help guide future studies of laboratory resist paradigms for alcohol and alcohol consumption in the field. The work of McKee et al. (2006, 2009, 2012) on impaired control in smoking is another valuable source when developing methodology for future version of Resist-CASE and other impaired control over alcohol paradigms.

When evaluating the findings for this exploratory aim, which uses data from RCASE as the predictor variable, it is important to note that changes that took place during the development of the pre-pilot and pilot phase of the protocol may have impacted data. (These considerations also apply to selected analyses in Specific Aim 2 that also used data from RCASE). Stated simply, because there was "evolution" in task

parameters (in RCASE), the 13 participants did not complete the identical paradigm (see Table 1).

Several of the changes could plausibly impact data and results and should therefore be noted. For example, one change in the pre-pilot and pilot phases of the protocol was the change from a linear earning schedule (McKee, 2009) to a de-escalating schedule (between 1 cent to 20 cents per minute of delayed drinking) during the Resist-CASE sessions. This de-escalation reinforcement schedule more accurately models the decrease in ability to resist drinking as time passes and is based on related work in tobacco use and eating high-calorie foods (Udo et al., 2013).

In addition, after inquiring with early stage participants about why they abstained from alcohol consumption, it became apparent that participants were not self-administering alcohol in order to complete the study as quickly as possible. This was due to the protocol safety requirements that participants stay in the NIH Clinical Center until their breath alcohol concentration returned to 0, often lasting several hours into the evening. In order to maintain safety requirements while minimizing the disincentive to drink, we amended the protocol to include an overnight stay in the NIH Clinical Center following alcohol self-administration, regardless of how much participants consumed.

There were also small changes to the EMA procedures (which could potentially impact all aims). In order to reduce the number of assessments that were self-initiated (which therefore decreased the randomness of the data), we changed the payment structure from $2 per assessment to $3 per completed random assessment and $1 for make-up assessments. This was also in keeping with our addition of a $5 charging bonus that was provided if the participant did not allow the study phone battery to die. Keeping

the study phone charged is essential to completing the study as a dead battery means there are no assessments being administered or completed. Further, when the study phone battery died, the EMA assessment software could encounter technical errors that are difficult or unable to be resolved while the phone is in the field.

The current study provides a foundation for further Resist-CASE paradigm exploration and development by establishing feasibility of combining a laboratory based CASE paradigm with a concurrent EMA protocol, as well as providing valuable information for continuing to develop the resist variant of the CASE paradigm. The current Resist-CASE paradigm is successful in capturing variability in drinking and resist behavior, with related data about motivation to cut back or stop drinking, but sample sizes need to increase in order for us to further examine the relationship between laboratory and EMA data as well as the variables examined in Specific Aims 1 and 2 and the additional exploratory aims. While the current study is limited to 16 participants (13 with RCASE data), the Resist-CASE protocol is continuing to run additional participants. Subsequent analyses of these additional participants will help to further establish the Resist-CASE paradigm or inform future changes. In summary, it is too soon in the development of this protocol to state that the paradigm works as intended.

Future variations of the current paradigm may further increase ecological validity. For example, self-administration sessions could take place in a simulated bar environment in the presence of other drinkers (participants or confederates) (Davidson, Swift & Fritz, 1996; Davidson, Palfai, Bird & Swift, 1999 as described in Leeman et al., 2013). While we did not ask participants to disclose if they were alone or in a social environment when completing EMA assessments, our controlled laboratory environment

was a relatively isolating experience by design to minimize influence of others. We may also consider not administering assessments during active drinking, whether in the laboratory or in the field to allow for a natural drinking behavior progression (Leeman et al., 2013). We may also consider including wearable technology to allow for another type of measurement, particularly for drinking behavior using wearable alcohol sensors (described in detail later).

Exploratory: Within-Subject Predictors of Drinking in the Field

As noted earlier, a number of significant within-subject associations were found in the EMA data. For example, as EMA alcohol craving increased, alcohol consumption assessed in the next EMA response increased, consistent with our hypothesis. Craving is considered a significant risk factor, and a potential treatment target, for relapse when attempting to cease alcohol use (see summary of related studies in Szeto, 2017 and Table 2; McKay & Hiller-Sturmhofel, 2011), and our findings are consistent with this literature base.

Moreover, there were significant within-subject associations between drinking goal/motivation and subsequent drinking. As EMA drinking goal increased (which is to cut down or stop drinking), alcohol consumption assessed in the next EMA response decreased, which demonstrates that intact executive cognitive processes could inhibit drinking. In other words, when the participant wanted to reduce or stop drinking, they were able to (to a certain extent), which indicates some ability to control their drinking behavior in this group of heavy binge drinkers.

There is a lack of research examining how drinking goal relates to drinking behavior as most research focuses on the role of craving, impulsivity, and impaired

control on drinking behavior. A study on impaired control over drinking in 39 college age frequent heavy drinkers did not find a relationship between the Impaired Control Scale self-reported impaired control and number of beers self-administered, estimated peak breath alcohol concentration during drinking, and post-drinking breath alcohol concentration (Leeman et al., 2013).

In addition, as motivation to stop drinking increased, alcohol consumption assessed in the next EMA response decreased, suggesting that when participants wanted to control their drinking, they were able to shape their behavior in the desired direction. This finding is consistent with the finding that as EMA drinking goal increased (which is to cut down or stop drinking), alcohol consumption assessed in the next EMA response decreased.

Motivation plays a significant role in drinking behavior however, we were unable to locate any studies that examine motivation and drinking behavior in a within-subjects multiple assessment study such as the present study. The present study contributes novel information about the motivation to cut back or stop drinking and subsequent drinking behavior. Other studies provide information that could help further develop the novel findings of the present study. A study of 200 undergraduate psychology students ages 17-63 completed online or paper and pencil forms about their alcohol use including type of motive for drinking, drinking expectancies, and coping styles (Hasking, Lyvers, & Carlopio, 2011). The authors conducted a hierarchical multiple regression and found that only avoidant coping was related to drinking behavior at step two, and that all alcohol expectancies other than change in cognition were related to drinking behavior at step three (Hasking, Lyvers, & Carlopio, 2011). Following step three, avoidant coping was no

longer related to drinking behavior, but the others had an effect size. In the fourth and final step, drinking behavior was related to all drinking motive types (Hasking, Lyvers, & Carlopio, 2011). Motive types are important to know as a complement to motivation in developing future versions of the present study.

Although we are not aware of any published EMA studies examining prospective associations between motivation to abstain and subsequent drinking, studies have examined the association between self-efficacy to remain abstinent and drinking. A genetic study of the effects of topiramate on daily drinking in 138 treatment-seeking heavy adult drinkers of European American descent examined the role of self-efficacy in drinking behavior (Kranzler et al., 2014; Kranzler et al., 2016). The authors called between 5:00-8:00pm nightly and asked participants to rate 0-4 their confidence in their ability to resist heavy drinking "for the rest of the night", as the treatment goal was reduction of heavy drinking (Kranzler et al., 2016). They found that when participants reported high self-efficacy levels, they drank less that night (Kranzler et al., 2016). This finding provides further evidence that impaired control and drinking goal are valuable areas for development of future protocols like Resist-CASE.

There is potential clinical utility from our predictor variable findings described above. For example, in light of our findings that craving and increases in drinking goal to avoid drinking were associated with drinking on the next EMA assessment, our data could help clinicians identify high-risk periods for alcohol use. Data on these periods of high-risk could be shared with the patient and treatment could be tailored to prevent these periods, develop early intervention at the beginning of the high-risk period, and develop approaches to intervene using EMI. Moreover, our finding that motivation to stop

drinking in the next 24 hours was associated with lowered EMA drinking on the subsequent assessment could identify periods where a strengths based approach to treatment development could be key. For instance, during these periods, resistance to engaging with treatment may be lower, providing an opportunity for approaches such as motivation interviewing, harm reduction, and referral to treatment to be initiated. Other healthy behavior change may be possible during this time and further research on the relationship between periods of high motivation to stop drinking and engagement in other patient driven goals is warranted.

STUDY LIMITATIONS

As noted repeatedly, the major limitation of the study was the small sample size (*n*=15 for Specific Aim 1), which was smaller than planned (*n*=37) and resulted in lower power for analyses than that anticipated (and reported earlier). The small sample size was largely due to the difficulty in recruiting participants who fit the inclusion and exclusion criterion as well the flexibility to attend several lab sessions while also completing daily EMA assessments. The study was highly complex and the data depend on the successful completion of prior weeks of the study. Difficulty in participant recruitment was the major limiting factor for this study.

Second, there was no external "check" on the validity of EMA data. This issue can be mitigated to some extent if the field data exhibit good internal reliability and validity. For example, within EMA data one might expect craving to correlate with drinking (which it did). It may be useful in future studies to validate EMA reports of drinking against estimates of consumption derived from sensors (described later).

Third, it is that possible that the age range of 21-60 is too broad, particularly as college age drinking and middle age drinking may have different motivators, patterns, and outcomes. For example, many college age individuals drink due to the presence of peers who are drinking in terms of offers of alcohol, social norming, and behavior modeling (Borsari & Carey, 2001). The current study does not examine or account for these different drinking motivators.

Fourth, the study's inclusion criteria for binge and heavy drinking may be too strict to capture the intended population and may limit variability. Further, there are no inclusion criteria for those wishing to cut down or stop drinking. This is in part due to the focus on non-treatment seeking samples that are at-risk of developing an alcohol use disorder, not those who are already in treatment targeted populations. One possible consequence of not targeting those motivated to cut back or abstain is the study may find people who delay self-administration for other reasons beyond the study's specific aims. For example, rather than measuring cognitive control, we may capture a person's novelty seeking behavior. Importantly, we could have participants who delayed self-infusion in the lab in order to earn money to be used on future alcohol purchases. One potential future modification would be to add a motivation measure to the set of assessments administered throughout CASE sessions, to include ICS perceived control to obtain a dynamic measure of the change.

Fifth, the EMA motivation questions may be limited in scope as the study uses just two questions (due to an attempt to minimize participant burden). The factor of motivation requires particular consideration in this study as we did not intend to recruit or

study a sample motivated for treatment as we sought to understand factors that lead to the development of alcohol use disorder.

Sixth, data collection for up to six weeks is an ambitious number of assessments. It is reasonable to expect that some participants may respond in a less robust and accurate manner over time. While this possibility is important to consider, the study design and analysis have been crafted to minimize the effects of participant burden over time.

Seventh, as data collection was designed to be gathered randomly over the course of a day, participants were empowered to select the wake up and bedtime time range and were able to delay or ignore random assessment prompts. As such, the time range across each day may vary by participant. For example, participant A may have a 16 hour potential window for random assessment presentation while participant B may have a 10 hour window for random assessment presentation. In an attempt to increase compliance and account for intrusion into participants' daily routine, we allowed for make-up assessments to take the place of random assessments. In order to incentivize completion of random assessments over make-up assessments, we increased payments to $3 when made in response to a beep and decreased payments to $1 when initiated at the participant's convenience. As such, the majority, but not the entirety of the assessments are randomly prompted by our software and algorithm. Most importantly, when participants employ make-up assessments in lieu of algorithm prompted random assessments, the data become less random, thereby undermining our ability to generalize our data to the full population of moments for each individual.

Eighth, all analyses are essentially correlational and it is not possible to extrapolate the causes of observed episodes of inability to resist in the lab or field data.

Finally, this study did not gather data on the role of the presence of drinking peers during field assessments. The presence of other drinkers and the context of the drinking environment may have influenced the participant's drinking behavior, and it would be useful to collect these data in future studies.

STUDY STRENGTHS

A primary strength of this study is it is the first study to examine impaired control of alcohol consumption both in the laboratory and field and it does so with innovative technology-forward methodology. It helps answer a need in the field for more data to support ecological momentary intervention (EMI) development. It provides data to help with field validation of the methods of the CASE paradigm. It also helps provide insight into momentary states that may increase risk for binge drinking, a key factor in the development of an alcohol use disorder. It also nicely merges the NIAAA's recent work on impaired control using the well-established CASE protocol in the lab, and LOCI's work on EMA in alcohol use.

The EMA methodology provided a large amount of repeated data that has allowed for complex multi-level analyses. This study produced a large rich dataset from the laboratory and field components over several laboratory visits and weeks of EMA. This data could have revealed patterns that could help tailor individual level treatment. The approach complemented McKee et al. (2006, 2009, 2012)'s work on impaired control of cigarette smoking. This study contributes to validating the laboratory model of impaired control and the findings are a significant step forward for research in this area.

FUTURE DIRECTIONS

This study will help inform further development of NIAAA's current self-administration of alcohol (CASE) paradigms. These paradigms are currently elegant, well-controlled, and highly replicated. However, it is not known how generalizable the CASE protocol is to the real world. We hope to continue to examine drinking behaviors modeled by the CASE lab procedures in the field by leveraging mobile technology, including mobile wearable devices that track physiological information such as blood pressure, heart rate, activity, and sleep. We also plan to pursue field studies that will gather alcohol consumption data using mobile breath alcohol sensing devices, as discussed in more detail later. Further studies may have larger sample sizes and may incorporate social and environmental cues in laboratory-based bar settings to better mimic the environment of most drinkers. Further down the road, employing a CASE model combined with an EMA model may assist with medication development. This study also adds to other growing bodies of research including wearable technology, digital phenotyping, ecological momentary interventions (EMI) and health apps; all are explored below. But first, several methodological and demographic considerations are explored to inform potential future adaptations to the present study.

Methodological Considerations

Before exploring potential additions to future direction of the study, several modifications to the current study are to be considered. Among them are adding questions to the EMA assessment and changes to the methodology of comparing lab and field.

Types of beverage consumed during EMA assessments may be particularly salient to consider assessing during EMA in future studies. For example, type of drink (beer, wine, or liquor) may influence the rate of consumption, particularly given the variation in

ethanol concentration (Masters, 2012). This addition might be helpful to consider when comparing lab derived BAC with EMA drinking data. Asking participants about type of drink could contribute to previous data suggesting that oral and IV self-administration of alcohol have similar breath alcohol exposure profiles (Plawecki et al., 2019). Further, the impact of adding a series of questions about type of drink should be considered in light of potential increases to participant burden.

If future research continues to find that EMA and lab measures fail to match, additional considerations can be made in light of Shiffman et al.'s study on cue reactivity (CR) and EMA drinking (2015). For instance, the authors considered that cues provided in a CR context may be overly simplified when compared to the complexity of real world cues, particularly if CR cues are not personalized by participant (Shiffman et al., 2015). Further, being in a controlled environment, such as the hospital room used in the lab portion of our study, may enhance a participant's reaction to being studied (Shiffman et al., 2015). Possibly most notably, lab paradigms may elicit significant anticipation of study measures and manipulations, an experience that may not be replicated in real world drinking (Shiffman et al., 2015). To help address these and other concerns that limit lab to EMA and vice versa findings, changing the environment of the lab study to further match natural drinking in the field should be considered. Among these options are placing lab consumption in a bar-like setting or using virtual reality to mimic natural drinking context, which has already been found in a review to effectively induce craving (Ghiţă & Gutiérrez-Maldonado, 2018). Technology to assist with research is readily emerging and holds promising opportunities for future research that builds off our study.

Generating typologies of subgroups of binge drinkers is an important consideration for future studies. A time series study of smoking behaviors to help address high relapse rates following smoking cessation found that novel data analytic approaches can help group patients using EMA data patterns (Hoeppner et al., 2008). Data may be nomothetic with few data points from many participants or idiographic analyses providing a deluge of data points per individual participant (Hoeppner et al., 2008). Theoretically, both types of data may suffer from limitations in generalizability and "population-level growth functions might fit the overall observed sample of individual growth patterns but fail to describe even a single individual's trajectory" (Hoeppner et al., 2008). These issues might be addressed by identifying sub-populations to conceptualize inter-individual differences in intra-individual change and identify trajectories (Dumenci & Windle, 2001 as cited in Hoeppner et al., 2008). By grouping individuals after data has been collected, data-driven patterns of change can complement theoretical considerations used in study design. Hoeppner et al. (2008) combined time series and dynamic cluster analyses of a variable measured on many occasions ("time series-based typology". They found that time series-based typology is sensitive to detecting trajectories that hold promise for developing effective sub-group based smoking cessation interventions (Hoeppner et al., 2008). Time series-based typology may be a useful approach to future research on binge drinking.

Demographic Considerations

Future versions of this study may focus on populations that have special considerations when addressing binge drinking. One potential population is American Indians, who have been found to have the highest rates of heavy alcohol use among

Americans over age 12 at 9.2% of respondents to a national survey (SAMHSA, 2015 September). As noted above in Alcohol Use and Health Disparities, American Indians have higher rates of liver cirrhosis (along with Latinos) (Zemore et al., 2018). As heavy alcohol use is associated with liver cirrhosis, American Indians with high-risk drinking are an ideal population to target with future CASE studies. Methodological considerations for targeting this group include the use of community-based participatory research (CBPR) methods (Collins et al., 2018). CBPR is a strengths-based, equitable, and collaborative approach with stakeholders including community members and researchers (Collins et al., 2018). Establishing these relationships may become easier as many tribal leaders have recognized substance use disorders as a considerable problem in their tribes, creating an urgency that may allow researchers outside of a community to help (Tan et al., 2008). Previous research regarding use of the DSM 5 diagnostic criteria for alcohol use disorder in American Indians has found it to be valid in a sample of treatment-seeking American Indians (Serier et al., 2019). Consideration of "aging out" of alcohol use disorders has been observed in certain American Indian drinkers, which may reflect cultural value of elders, or motivation to stop due to the loss of drinking companions (Grella & Greenwell, 2004; Westermeyer et al., 2008), should be considered when crafting inclusion criteria. Other cultural variables should be explored and considered when adapting a study such as ours to a specific population such as American Indians.

Wearable Technology

Beyond combining CASE with EMA, adding non-invasive wearable tools such as breathalyzers, actigraphy, heart rate, skin conductance, and light sensors, accelerometers,

and sleep trackers to other studies can increase validity of measures across collection methods (Ferreri et al., 2018; Marsch, 2012). Additional ambulatory monitoring techniques for substance use research include global positioning systems (GPS) used to provide information on the participant's immediate environment and collection of biological samples (saliva, perspiration, breath) in the field (Bertz, Epstein, & Preston, 2018). Adding wearable technology to a study such as this dissertation project would add precise unbiased biological field measurements that rival the highly controlled lab based CASE methodology while including valuable self-report and cognitive bias data. More specifically, adding wearable alcohol monitors to the EMA portion of a CASE study would allow for the collection of field data that would mirror the lab based breathalyzer time points that take place during CASE and resist CASE visits. Further, wearable tools can combine specific timestamped data with self-reported EMA assessments that were completed at the same time to help contextualize behavior and mood responses (Bertz, Epstein, & Preston, 2018).

The addition of wearable technology to studies is an approach that supports NIAAA scientists' initiative to develop personalized medicine approaches to treat alcohol use disorders, which is in line with initiatives to develop personalized medicine across the National Institutes of Health (Gao et al., 2016; National Institute on Alcohol Abuse and Alcoholism, 2015; National Institutes of Health, n.d., *Personalized medicine*). Dr. Ramchandani's group has already begun testing non-invasive wearable alcohol monitors in three configurations: wrist watch, temporary tattoo/patch, and a button placed on clothing near the participant's neck that can detect breath alcohol levels. In addition to testing the accuracy of the various alcohol sensors, Dr. Ramchandani's group is testing

the participant's subjective experience and tolerability of wearing the devices for several hours of lab based testing using the CASE model. Particular attention is paid to the participant's local irritation or reaction as well as additional participant burden. With thoughtful incorporation into existing and upcoming studies, wearable monitors will enhance research outcomes and could lead to more effective prevention and treatment strategies (Marsch, 2012). Finally, wearable devices may play a key role in helping contain rising treatment costs (Mukhopadhyay, 2015) and reduce self-monitoring reactivity.

Digital Phenotyping

Another avenue for future research is developing early detection tools for mental health concerns that can disrupt the development of psychopathology. Early detection of signs of mental health deterioration can help clinicians initiate preventative steps that could reduce the likelihood of developing chronic or severe outcomes down the line. A high profile start-up company is currently studying how digital phenotyping could be used as a correlate with measures of brain activity, cognitive functioning, and clinical symptoms (https://mindstronghealth.com/). One of the co-founders of the start-up recently published a paper examining potential digital biomarkers associated with cognitive function. Dagum (2018) defines digital biomarkers as distinct measurements made up of repeated series of actions on a smartphone (e.g. tapping delete twice in a row). He found that over seven days of use 27 participants aged 18-34 several factors predicted scores on a battery of frequently used neuropsychological measures. A different research group has defined digital phenotyping as quantification of momentary data from digital devices from the level of the individual human phenotype (Torous, Kiang, Lorme,

& Onnela, 2016). This group also differentiates active data such as interactive surveys from passive data like GPS travel information (Onnela & Rauch, 2016). Differences in how these two groups of researchers define digital phenotyping suggests that there is much consensus to be had through future development of this area of research. Yet another group studied digital phenotyping that captured frequency, duration, and intensity of suicidal thoughts using EMA methodology to delineate five distinct phenotypes (Kleiman et al., 2018).

One of the major proposed benefits of this type of research is that it is measuring repeated occurrences of behavior associated with ubiquitous interactions between a person and a smartphone without intrusive measures. These data are gathered below the level of consciousness innate in self-report data and is depersonalized, which reduces potential security and privacy concerns of traditional data collection. For highly stigmatized behaviors such as chronic suicidality, risk-taking, and substance misuse, data collection may have fewer barriers to achieve larger and more complete datasets. From a theoretical lens, using digital phenotyping may help health and mental health professionals reduce bias in their clinical decision-making (Hsin et al., 2018), particularly in cases where effective tools and medications have yet to be found, understood, or implemented. Further, digital phenotyping has potential to focus on promoting mental health similar to how technology such as Fitbit promotes physical activity and health (Onnela & Rauch, 2016).

Digital phenotyping may also be combined with electronic medical records, molecular data, and neuroimaging data to combine data from different sources and which may enhance personalized or precision medicine (Torous, Kiang, Lorme, & Onnela,

2016). The Onnela Lab at Harvard has developed a research platform called Beiwe that combines a smartphone app, database capabilities, a study portal, and data analysis/modeling tools to help gather data and detect patterns over time (Torous, Kiang, Lorme, & Onnela, 2016). Multifunctional platforms like Beiwe are already being implemented to help EMA data to be used in digital phenotyping. When considering how to employ digital phenotyping, particularly when used in conjunction with EMA, appropriate statistical methods must be used. When using digital phenotyping data, many researchers choose to use generalized estimating equations (GEE) when the outcome distribution is not certain. Barnett et al. (2018) caution that GEE is not always the appropriate statistical approach, especially in cases where data include large numbers of observations per participant. They further suggest that generalized linear mixed models can help improve overall accuracy "when model misspecification is not severe." (Barnett et al., 2018). Onnela and Rauch (2016) suggest that phenotyping data remain raw and that, while complex large datasets can be summarized in many ways, specific scientific questions and thoughtful statistical considerations guide analyses. They predicted that digital phenotyping data will use combined statistical tools and machine learning (a computer's ability to learn without being intentionally programmed; Ferreri et al., 2018)) to develop insights into biomedical and clinical applications. EMA could also be combined with digital phenotyping for future studies.

A contrast between EMA and digital phenotyping is warranted to understand where research has been well-established in EMA and where research in digital phenotyping has the potential to go. EMA requires active data collection (e.g., completing surveys), whereas digital phenotyping can rely exclusively on passive

behavioral data using mobility and spatial patterns as well as social dynamics as data (Onnela & Rauch, 2016). Digital phenotyping has been conceptualized as requiring smartphone technology (Onnela & Rauch, 2016), whereas EMA can be gathered using palm pilots or standard cell phones (Waters & Li, 2008). Consequently, digital phenotyping has the potential to gather huge amounts of data at a larger population level, including the capacity to use passive data to initiate smaller surveys tied to targeted locations or events (Onnela & Rauch, 2016).

Ecological Momentary Intervention

Mobile intervention is another related and promising area for future research. Ecological momentary intervention (EMI) is the practice of administering field-based interventions on a mobile device to change targeted behaviors. EMI can be administered in many forms including SMS messages, behavioral change promotion, psychoeducation information, motivational messages, and real-time coping strategies (Ferreri et al., 2018). The intervention is delivered contingent of participant responses, "just-in-time". EMI is the natural extension of EMA and has been studied for many behavioral concerns, including alcohol misuse (Collins, Kashdan, & Gollnisch, 2003), and promises to be a significant method of the future. Many EMI studies have focused on addressing high-risk drinking in drinkers in the 18-25 range, often coinciding with college drinking.

Riordan and colleagues conducted a study of EMI effectiveness in reducing drinking in college students in New Zealand beginning with their first week of college often termed Orientation Week (Riordan, Conner, Flett, and Scarf, 2017). Their goal was to disrupt early hazardous drinking patterns to help students avoid heavy drinking throughout the academic year. To begin this task, they created small focus groups of

participants from a prior similar EMI study (Riordan, Conner, Flett, & Scarf, 2015) to help tailor their EMI SMS message content and timing. The results from the focus group were that to be effective, messages should: focus on social approaches rather than health messaging, use slang or colloquial tones, use text message rather than Facebook or an app. In order to be most effective with time, messages should be sent earlier in the day before heavy drinking begins and more than once a day (but not every day). The students in the focus groups also highlight how they may not have consumed alcohol before college, but they felt immense peer pressure to drink during Orientation Week, validating the researcher group's approach to focus on the first week of college drinking in order to help shape drinking behavior throughout the year. After administering an EMA + EMI condition during Orientation Week, drinking was reduced when compared to the EMA condition both during Orientation Week and into the first semester of college (Riordan, Conner, Flett, and Scarf, 2017).

A similar study that took place in Australia conducted focus group development workshops to help design the study and investigate the feasibility of administering an EMA and EMI study during a single drinking episode (e.g., while the participant has been drinking) (Wright et al., 2016). The participant chose a drinking night within a two-week period, selected the start time for surveys to begin, and completed a pre-drinking survey that provided the option for the participant to write a message to be sent to their future (potentially intoxicated) self. If they did not create a message, they were sent an SMS message from the researcher based on their answers to the hourly questionnaires and tailored by gender, their self-reported goal and plan for the night of drinking, amount of alcohol already consumed, amount spent, location, and priorities that relate their

drinking motivation. Following the EMI from their night out drinking, the participants were debriefed and were asked for extensive feedback focused on feasibility and tolerance of the study methods. They found an 88% response rate and that adding EMI to the EMA portion of the study did not affect participation (Wright et al., 2016). A 2013 study used SMS messages to target hazardous binge drinking in young adults who had recently been seen in the emergency room (Suffoletto et al., 2013). The intervention group received 12 weeks of SMS messages that shared the health consequences of alcohol consumption, personalized feedback, protective strategies for drinking, and support for goal setting. The primary outcome was number of binge drinking days in the prior month, and these were on average one fewer binge drinking in the EMI intervention group when compared to control (Suffoletto et al., 2015). The authors of this study also completed a focus group with study participants who were part of the intervention group and found that these factors were important when developing EMI: comfort, confidentiality, ease of use, and increased awareness of and accountability for drinking behavior (Suffoletto et al., 2016).

Further extending this line of work using the Texting to Reduce Alcohol Consumption 2 model, Suffoletto et al. (2018) examined an SMS message intervention that allowed for adaptive goal setting by the participant for a voluntary period of enrollment in the study in increments of four weeks. This group found reductions in drinking from baseline to three months, but reductions were not based on length of enrollment in the four week EMI periods. Another group conducted a randomized control trial in Australia that included web-based EMA with text-based feedback as an intervention for 269 young adults who endorsed risky drinking behavior (Wright et al.,

2018). This group found that EMA and control groups had slight nonsignificant decrease in drinks consumed during the most recent heavy drinking episode and no decrease in the EMI group. Of note, this group tracked technical errors in presentation of EMA and EMI and found that many participants struggled with providing information or receiving EMI messages when attempting to participate in the study. This information is helpful when considering EMI design in future studies.

Digital Health Applications

According to Bates et al. (2018) health apps have enormous potential to reduce costs and increase access to health care support and interventions, making them medical devices in the form of software (Shuren et al, 2018). In order to regulate health apps and protect user safety and privacy, the US Food and Drug Administration is starting a precertification program (FDA, 2018). It remains to be seen whether this program accomplishes its goal of providing "streamlined and efficient regulatory oversight of software-based medical devices" (FDA, 2018). The digital health application development space is at the cutting edge of patient interaction, but the research base remains to be built. One forthcoming study is focused on using the Substance Abuse Research Assistant (SARA) app to increase and retain adherence to EMA collection by using strategies such as visually appealing interfaces, engaging content, and additional monetary and in-app rewards for high compliance (Rabbi et al., 2018). Once published, this data may help inform app development, but also ways to increase compliance in all digital data collection and intervention strategies.

While much of the intersection of EMA, digital phenotyping, EMI, and healthcare apps remains to be explored, one recent study has started charting the course. Bae at al.

(2018) employed phone sensor data and machine learning to identify alcohol use with the goal of informing EMI. They provided 30 young adult heavy drinkers with an app for 28 days during which each participant self-reported their alcohol consumption (Bae at al., 2018). Drinking occasions were classified as low-risk or high-risk (binge drinking). The authors found the most useful sensor information indicated day of week and time of day of consumption, change in movement, device usage time, and communication characteristics (duration of a phone call or typing speed) (Bae at al., 2018). Using these factors and the self-report data in a period as short as 10 days, the authors reported being 90% accurate in predicting periods of high-risk alcohol consumption following 30 minutes of onset of drinking (Bae at al., 2018). This technological advance would allow for targeted EMI in a more ecologically valid model than the Wright et al. (2016) paper described above where the participant selected one drinking night within a two week time period and responded to EMA and received EMI as they drank. Our study builds off of work described in the previous paragraphs and can encourage and inform future research to continue to leverage the power of digital technology in developing interventions for excessive alcohol use.

Table 1. Review of Studies of Impaired Control/Ability to Resist

Study & Design	Purpose of Study	Participants	Methods	Relevant Dependent Variables	Analysis	Main Findings
Kahler et al. (2014) Experimental	Investigate the effect of alcohol consumption on smoking lapse behavior	100 heavy alcohol drinkers smoking 10-30 cigarettes daily	Placebo vs. low dose (0.4g/kg) vs. high dose (0.8g/kg) alcohol after 3 hours of smoking abstinence and 35 minutes later offered opportunity to smoke	-Urge to smoke -Stimulating effects of alcohol -Sedating effects of alcohol	Generalized estimating equations to test experimental condition on latency to initiate smoking during delay period	-Alcohol can reduce ability to resist smoking -Alcohol increases intensity of urge to smoke
Leeman, Corbin, Fromme (2009) Experimental	Examine whether craving only occurs when access to alcohol is blocked & whether craving mediates associations between personality traits & AL drinking	174 21-30 year old moderate to heavy drinkers (women: 4+ men: 5+ drinks once in prior month)	Groups of 2-4 had 10 mins to consume 3 drinks in a simulated bar with a 15 min absorption period after 3rd drink followed by 20 mins AL period. Alcohol vs. taste-masked placebo	-Craving -AL Consumption	2x2 ANOVAs to test differences in AD consumption, weekly consumption, craving, personality by condition and gender Hierarchical multiple regression analyses used to test craving & personality traits as predictors of AL Baron & Kenny approach for mediation analyses	-Trait disinhibition and craving after placebo (not alcohol) significantly predicted AL consumption -Both conditions reported similar craving levels -Craving partially mediated associations between trait disinhibition & AL consumption

					All analyses repeated using MLM	
Leeman et al. (2013) Experimental	Establish internal validity of impaired control lab paradigm	21-25 year olds who drink alcohol twice per week	In bar setting, participants allowed to drink as many beers as desired during 3 hours up to max eBAC Impaired experimental condition: moderate drinking guidelines ("Consume no more than 3 drinks (2 for women) during ad libitum drinking period) and probabilistic payment reductions (to model consequences of alcohol use) following performance on cognitive/psychomotor tests 1-3 days after alcohol self-admin	-4 cognitive/psychomotor tasks -Amount alcohol consumed	Planned primary and secondary analyses to compare self-adm of alcohol and placebo, post hoc analysis of study conditions, mechanistic analyses to examine approaches moderate drinkers used to limit use, exploratory	-Experimental condition participants were: more likely to self-administer at least 1 nonalcoholic drink, longer drink durations, longer intervals between 2nd and 3rd beers, lower BAC on average, less likely to meet heavy drinking criteria -
Leeman et al. (2014) Experimental	Impulsivity and subjective response to IV alcohol	105 non-alcohol dependent social alcohol drinkers between 21-30 years old	Self-reported impulsivity (BIS), ethanol dose condition (high or low dose, or placebo) and time during IV self admin -60 mins clamped alcohol within 5mg of target state (100mg% or 40mg% or placebo)	-Self reported impulsivity -Stimulant and sedative response	Checked normality for continuous variables, subjective responses were heavily skewed so used parametric approach	-High impulsivity individuals: elevated stimulant and dampened sedative response to alcohol, particularly at higher dose, steeper increase in stimulant effects during first half of clamped ethanol infusion at higher dose

			-3 sessions, three days apart, double-blind, randomized			
Leeman, Beseler, Helms, Patock-Peckham, Wakeling, Kahler (2014) Review	Review of impaired control alcohol research in epidemiology, measurement issues, potential mechanisms underlying impaired control & problem drinking	Examined studies in terms of: epidemiology, measurement issues, potential mechanisms between impaired control and alcohol consumption	n/a	n/a	n/a	-Impaired control can be an early indicator of alcohol dependence development. As dependence persists, a shift from impulsive to compulsive use including impaired control -Multi-item self-report scales are useful to include varying levels of impaired control -Future studies need to examine impulsivity as well as family history/genetic background of person who exhibits impaired control
McKee et al. (2006) Experimental	Examine role of alcohol use in smoking lapse behavior 1)Does alcohol facilitate initiation of 1st cigarette? 2)Once 1st cigarette is initiated, does alcohol facilitate subsequent smoking?	16 daily smokers (15 daily) who are also heavy social drinkers (twice per week, 3+ men, 2+ women) 21-55 years old	Within subject design Priming dose alcohol (0.03g/dl) or placebo Two 6.5 hour lab sessions Option of initiating 1 hr tobacco self-administration session (with $ reinforcer for cigarettes not smoked) or delaying initiation by 5 minute increments up to 50 mins for up to $10 reinforcer; each cigarette cost $1 of total $8 smoking tab paid at end of session	-Primary outcomes: Length of delay period, # cigarettes during AL -Secondary outcomes: Alcohol craving, tobacco craving, subjective reactivity to alcohol, nicotine withdrawal	Within subject Paired t-tests for primary outcomes Secondary outcomes: MANOVA, Pearson correlation coefficients for exploratory Repeated analyses with gender as between subject factor	-Priming dose of alcohol vs. placebo decreased time to initiate smoking when proportional monetary reinforcement was provided as delay of smoking increased -After alcohol, less able to resist the 1st cigarette and initiated smoking sessions sooner, smoking more cigarettes (vs. placebo)

Note: AL= ad libitum drinking, MLM= multilevel models

Table 2. Review of Studies Comparing Laboratory and EMA Data

Study & Design	Purpose of Study	Participants	Methods	Relevant Dependent Variables	Analysis	Main Findings
Litt et al. 2000 Experimental	Identify predictors of alcohol craving (drinking cues) & relationship between craving and drinking after treatment; examine negative affect and dependence on urge to drink in lab CR	N=26, average age 50.6 year old men in in/out patient alcohol treatment at VA	Lab: 2 CR sessions + drinking guided imagery script read by a research assistant EMA: Recorded drinking, craving, triggers/environment (access to alcohol, emotional state) & mood 8 times daily (60 seconds each time) for 21 days (paid $5/day if 2 RAa completed)	Alcohol abstinence self-efficacy scale (temptation to drink, confidence to resist drinking) Alcohol consumption	Correlation of lab craving with field measures/drinking Exploratory correlation of CR lab and field with individual (demographics etc) Mixed model logistic regression to predict field craving Stepwise discriminant function analysis to examine urge vs no-urge reporter	-Lab reported urge to drink correlated modestly with field urge and drinking frequency -Field urge and craving correlated with drinking -Predictors of field craving: week of recording (decrease over time), negative high arousal mood (angry, nervous), being at home/work/friend's house -When compared to EMA, retrospective reports of drinking underestimated drinking days -Drinking did not deteriorate monitoring quantity, but quality change is unknown
Ramirez & Miranda 2014 Experimental	Examine craving in adolescent drinking	N=42, 15-20 year olds who drank 2+ times per week in prior 30 days who could read simple English	Lab: CR paradigm (water vs. alcohol) EMA: Field alcohol cues (bottle/glass or tv/ads or no cues)	Alcohol consumption	Unstructured covariance matrix to examine craving events and average craving. Autoregressive AR1 structure to examine whether craving predicted drinking and to examine whether	-Alcohol cues elicited lab & field craving -Craving predicted drinking in the field

					lab CR predicted field CR.	
Shiffman et al. 2015 Experimental	Investigate whether lab cue reactivity correlates with field craving and smoking response to cues	N=190 daily smokers not trying to quit	Lab: smoking, alcohol, negative & positive affect, smoking prohibition cues EMA: 3 weeks RAs on environment, affect, craving in smoking & non-smoking events	Cue response (drinking), craving	2 step hierarchical approach: EMA within subject correlations from level 1 and between subject regressions predicted EMA correlations from lab CR	-Variety of cue responses made lab vs. field comparisons possible -Average 70 smoking RAs, 60 non-smoking RAs -Lab CR did not correlate with EMA field responses (0.03 average, none beyond 0.32, one of 40 correlations were significantly greater than 0)

Notes: CR= cue reactivity, RA= random assessment

Table 3. Differences Between Pre-pilot and Pilot Phase

Type of Change	Pre-pilot	Pilot
Stroop	None	Included in each assessment
Overnight stays	None	Required after each CAIS session
EMA $3 vs $1	All assessments $2	RA $3 Make-up $1
EMA charging bonus	None	$5
Number CASE visits	Baseline and two RCASE self-administration lab sessions (2 visits)	Baseline and two RCASE self-administration lab sessions (3 visits)
Number Prime Button Presses	4	6
Monetary Reinforcer	Linear earning schedule	De-escalating scale (.20-.01¢/minute)
Prime/No Prime Condition	Prime only	Prime and no prime
EMA duration	2-4 weeks	Up to 6 weeks
Study Payment excluding EMA and monetary reinforcer	$700	$980

Table 4. CASE & Resist CASE. Alcohol and No Prime conditions are completed in counterbalanced order

Lab Model	**Prime**	**Phase**	**Task**	**Variable for Analysis**	**Target**
Resist CASE	Alcohol Prime (vs. No Prime)	Delay	Self-Administer Alcohol *or* Earn Money to resist alcohol	Resist (Proportion of Time Resisted)	Failure to Avoid Drinking
CASE		Free Access	Self-Administer Alcohol Ad-Libitum	Lab Consumption (BRAC)	Recreate a Typical Drinking Experience

Table 5. Study Overview and Timeline

Lab Visit→	**1**	**2**		**3**		**4**		**5**		**6**		**7**
Location→	**Lab**	**Lab**	**Field**	**Lab**	**Field**	**Lab**	**Field**	**Lab**	**Field**	**Lab**	**Field**	**Lab**
	Screen	Base		AP		NP		FU		FU		FU
Inclusion/Exclusion/Demographi	X											
Brief Intervention												X
CASE		X										
Resist CASE				**X**		**X**						
EMA			**X**		**X**		**X**		**X**		**X**	
EMA MEASURES												
Perceived Control			**X**		**X**		**X**		**X**		**X**	
Alcohol/Tobacco Use			**X**		**X**		**X**		**X**		**X**	
Alcohol/Tobacco Craving			**X**		**X**		**X**		**X**		**X**	
Abstinence Motivation			**X**		**X**		**X**		**X**		**X**	
Drinking Goal			**X**		**X**		**X**		**X**		**X**	
Stroop task			**X**		**X**		**X**		**X**		**X**	
Hangover			X		X		X		X		X	
Mood			X		X		X		X		X	
LAB MEASURES												
Impaired Control Scale		X		X		X						
Subjective Units of Distress		X		X		X						
Timeline Followback	X	X		X		X		X		X		X
CASE Experience Questionnaire		X		X		X						
Profile of Mood States		X		X		X		X		X		X
Brief Biphasic Alcohol Effects		X		X		X						
Alcohol Urge Questionnaire		X		X		X						
Drug Effects Questionnaire		X		X		X						
Neuropsychological Assessment	X											

Note: Study Design and Laboratory Measures for Parent (Lab Study) and Proposed (EMA) Studies. Bolded measures are central to the current study. AP = Alcohol Prime; NP = No Prime (order counterbalanced). FU = follow-up. Each EMA period is 1 week except the last one which is 2 weeks (making 6 weeks of EMA in total).

Table 6. Demographics and Baseline Characteristics

		All
		N_2=16
Age (years)		35.13 (11.72)
Gender (%)		
	Male	88%
	Female	13%
Race (%)		
	White	62.5%
	Black	37.5%
Ethnicity (%)		
	Hispanic/Latino	12.5%
	Not Hispanic/Latino	87.5%
Education (years)		15.31 (2.36)
Income (1-9 scale)		5.81 (2.71)
90 Day Drinking History (TLFB)	Total Drinks	374.91 (135.81)
	Drinking Days	65.81 (17.44)
	Drinks/Drinking Day	5.82 (1.97)

AUDIT		16.06 (4.99)
Number of Criteria for Alcohol Use Disorder (Structured Clinical Interview for DSM-5 (SCID-5))		0.94 (0.25)
Impaired Control Scale (ICS)	Attempted (past 6 months)	7.56 (2.76)
		16.38 (7.27)
	Failed (past 6 months)	13.50 (6.53)
	Perceived	
Impulsivity (BIS)	Total	63.75 (9.12)
	Attentional Impulsiveness	9.81 (2.14)
	Motor Impulsiveness	15.50 (3.56)
	Non-Planning	23.94 (4.82)
Delayed Discounting (In_K)	Log of K	-3.61 (1.42)
Impulsive Behavior Scale (UPPS_P)	Urgency	2.09 (0.48)
	Premeditation	2.06 (0.50)
	Perseverance	1.93 (0.35)
	Sensation Seeking	3.04 (0.56)
	Positive Urgency	1.94 (0.54)

Table Note: Date are Mean (*SD*) (continuous variables) or % (Categorical variables). Average income translates to <$5000 per year for category 1, $5,000-$9,999 for category 2, $10,000-$19,999 for category 3, $20,000-$29,999 for category 4, $30,000-$39,999 for category 5, $40,000-$49,999 for category 6, $50,000-$74,999 for category 7, $75,000-$100,000 for category 8, and >$1000,000 for category 9. Missing data limited sample for Drinks Per Week, Number of Binges, and Average Binges Per Week to N=12. ICS All N_2 =16; BIS N_2 =16

Table 7. Summary Statistics of EMA Measures

Time →		**All**	
		N_I=954	
Variable ↓	Scale	N_I	
Compliance		954	60.56 (30.16)
			77.64%
Drinking Goal	1-3	954	
	Maintain Normal Drinking Pattern		61.43%
	Cut Down Drinking		24.11%
	Avoid Drinking Altogether		14.47%
Motivation 1 (Cut Down)	1-5	954	2.08 (0.93)
Motivation 2 (Stop)	1-5	954	1.96 (0.85)
Alcohol Consumption Quantity	1-5	954	1.66 (0.31)
Alcohol Craving	1-5	954	1.58 (0.50)
ICS Perceived Control 1 (Start Drink)	No	954	77.67%
	Yes		22.33%
ICS Perceived Control 2 (Stop Drink)	No	954	17.61%

	Yes		82.39%
Bored	No	954	79.45%
	Yes		20.55%
Sad	No	954	90.46%
	Yes		9.54%
Angry	No	954	87.74%
	Yes		12.26%
Anxious	No	954	80.61%
	Yes		19.39%
Good Mood	No	954	18.13%
	Yes		81.87%
Stress	1-5	954	1.57 (0.37)
Tired	1-5	954	1.65 (0.38)
Negative Affect (Angry, Sad, Anxious)	Endorsed none	954	72.01%
	Endorsed one		17.71%
	Endorsed two		7.34%
	Endorsed three		2.94%
Hangover	1-5	954	1.19 (0.25)

Smoking	1-5	954	1.23 (0.48)
Cigarette Craving	1-5	954	1.14 (0.20)
Classic Stroop	Ms	220	154.03 (126.89)
Drug Stroop	Ms	220	-2.39 (11.03)

Table Note: Data are Mean (SD). N_1 = no. assessments. Only complete assessments are included.

Table 8. Summary Statistics for Lab Measures

CASE Infusion Visit →		**Free Access**	**N**	**Primed (Session 2)**	**N**	**Unprimed (Session 3)**	**N**
Variable ↓	Scale/Subscale		N_2=16		N_2=16		N_2=16
Resist	Y	n/a		n/a	5	n/a	
Total EtOH consumed	Grams	59.54 (31.05)	15	16.05 (11.39)	13	29.38 (25.70)	4
Peak breath alcohol concentration	mg%	91.22 (43.00)	15	35.53 (39.53)	13	76.93 (43.64)	4
Number of infusions received		18.13 (6.81)	15	7.00 (9.18)	13	13.50 (9.04)	4
Delay in proportion of minutes	0-1	n/a		0.62 (0.41)	13	n/a	
Craving (AUQ Totally Baseline)	8-56	20.73 (11.26)	15	12.67 (4.04)	13	17.50 (10.63)	4
Craving (AUQ Total Peak)	8-56	28.00 (8.87)	15	24.38 (8.14)	13	25.75 (11.30)	4
DEQ	Peak Like	71.60 (15.44)	15	59.38 (23.60)	13	69.50 (15.61)	4
	Peak Want	65.87 (19.95)	15	49.08 (29.75)	13	75.50 (33.84)	4
	Peak High	44.40 (28.43)	15	39.54 (28.64)	13	50.00 (28.33)	4
	Peak Feel	46.13 (29.81)	15	35.54 (26.17)	13	40.00 (25.14)	4

Table Note: Data are Mean (*SD*). N_2=number of subjects; Each button press is 7.5mg% increase in breath alcohol concentration over 2.5 minutes.

Table 9. Results for Specific Aim 1

DV →						**EMA Alcohol Consumption (1-5)**				
IV ↓	**DV ↓**	***H***	***N₁***	***N₂***	*df*	PE	SE	F	*p*	95% CI
Lab Measures as Predictors										
Total EtOH consumed free access (LMM)	EMA	1.1	954	15	1,12.638	0.002817	0.003	0.804	0.387	-0.003, 0.010
Total EtOH consumed free access (Neg Bin)	EMA	Supp.	954	15	1, 921	0.001	0.001	0.520	0.471	-0.001, 0.003
Motivation as Moderator										
Motivation x Total EtOH consumed free access (LMM)	EMA	1.2	954	15	1, 315.427	-0.001	0.004	0.004	0.948	-0.007, 0.007
Motivation x Total EtOH consumed free access (Neg Bin)	EMA	Supp.	954	15	1, 919	-0.002	0.002	2.187	0.140	-0.006, 0.001

Table Note: N_1 = number of assessments; N_2 = number of subjects. *PE* = parameter estimate; *SE* = standard error; *F* = *F* value from LMM. Covariates are Day and Gender (parameter estimates for covariates not shown)

Table 10. Results for Specific Aim 2

DV →						**Alcohol Consumption**				
IV ↓	**DV ↓**	***H***	***N₁***	***N₂***	*df*	PE	SE	F	*p*	95% CI
Lab Measures as Predictors										
Lab Perceived Control	Lab*	2.1 First	n/a	13	1, 10	-1.00	0.66	2.28	0.161	-2.46, 0.47
Barratt Impulsivity Scale	Lab*	2.2 First	n/a	13	1, 10	-0.80	0.35	5.20	0.046	-1.59, -0.02
Delayed Discounting	Lab*	2.2 First	n/a	13	1, 10	-2.21	2.46	081	0.391	7.70, 3.28
Lab Perceived Control (LMM)	EMA**	2.1 Second	952	16	1, 12.26	0.022	0.013	2.745	0.123	-0.007, 0.050
Lab Perceived Control (Poisson)	EMA**	Supp.	952	16	1, 11.59	0.013	0.008	2.48	0.14	-0.005, 0.03
Barratt Impulsivity Scale (LMM)	EMA**	2.2 Second	952	16	11.819	0.010	0.009	1.262	0.284	-0.010, 0.030
Barratt Impulsivity Scale (Poisson)	EMA**	Supp.	952	16	1, 11.22	0.006	0.006	1.23	0.29	-0.006, 0.018
Delayed Discounting (LMM)	EMA**	2.2 Second	952	16	11.312	-0.023	0.055	.182	0.677	-0.143, 0.096
Delayed Discounting (Poisson)	EMA**	Supp.	952	16	1, 11.5	-0.01	0.03	0.15	0.71	-0.087, 0.06

Table Note: N_1 = number of assessments; N_2 = number of subjects. *PE* = parameter estimate; *SE* = standard error; *F* = *F* value from LMM. Covariates are Day and Gender (parameter estimates for covariates not shown)

*Total EtOH consumed during prime visit 2
**Alcohol consumption since the last assessment

Table 11. Exploratory Analyses: Resist

DV →				**EMA Alcohol Consumption (1-5)**					
IV ↓	**DV ↓**	***N₁***	***N₂***	*df*	PE	SE	F	*p*	95% CI
Lab Resist in Proportion of Minutes	EMA	803	13	1, 5.418	0.187	0.208	0.811	0.406	-0.336, 0.711
EMA Motivation as Moderator									
Motivation x Lab Resist in Proportion of Minutes	EMA	803	13	1, 235.722	-0.158	0.293	0.291	0.590	-0.736, 0.420

Table Note: N_1 = number of assessments; N_2 = number of subjects. *PE* = parameter estimate; *SE* = standard error; *F* = *F* value from LMM. Covariates are Day and Gender (parameter estimates for covariates not shown).

Table 12. Additional Exploratory Analyses

DV →					**Lead EMA Alcohol Consumption (1-5)**				
IV ↓	**DV ↓**	N_1	N_2	*df*	PE	SE	F	*p*	95% CI
EMA Deviation Scores as Predictors									
Deviation EMA Alcohol Craving	EMA	936	16	1, 2066.049	0.209	0.077	7.356	0.007	0.058, 0.359
Deviation EMA Negative Affect	EMA	936	16	1, 6.939	-0.043	0.059	0.526	0.492	-0.183, 0.097
Deviation EMA Drinking Goal	EMA	936	16	1, 115.659	-0.232	0.100	5.375	0.022	-0.430, -0.034
Deviation EMA Motivation 1	EMA	936	16	1, 8.934	-0.141	0.065	4.741	0.058	-0.288, 0.006
Deviation EMA Motivation 2	EMA	936	16	1, 4.567	-0.205	0.063	10.503	0.026	-0.372, -0.038

Table Note: N_1 = number of assessments, each reduced by one due to impact of creating a lead variable (the first assessment is eliminated); N_2 = number of subjects. *PE* = parameter estimate; *SE* = standard error; *F* = *F* value from LMM. Covariates are Day and Gender (parameter estimates for covariates not shown).

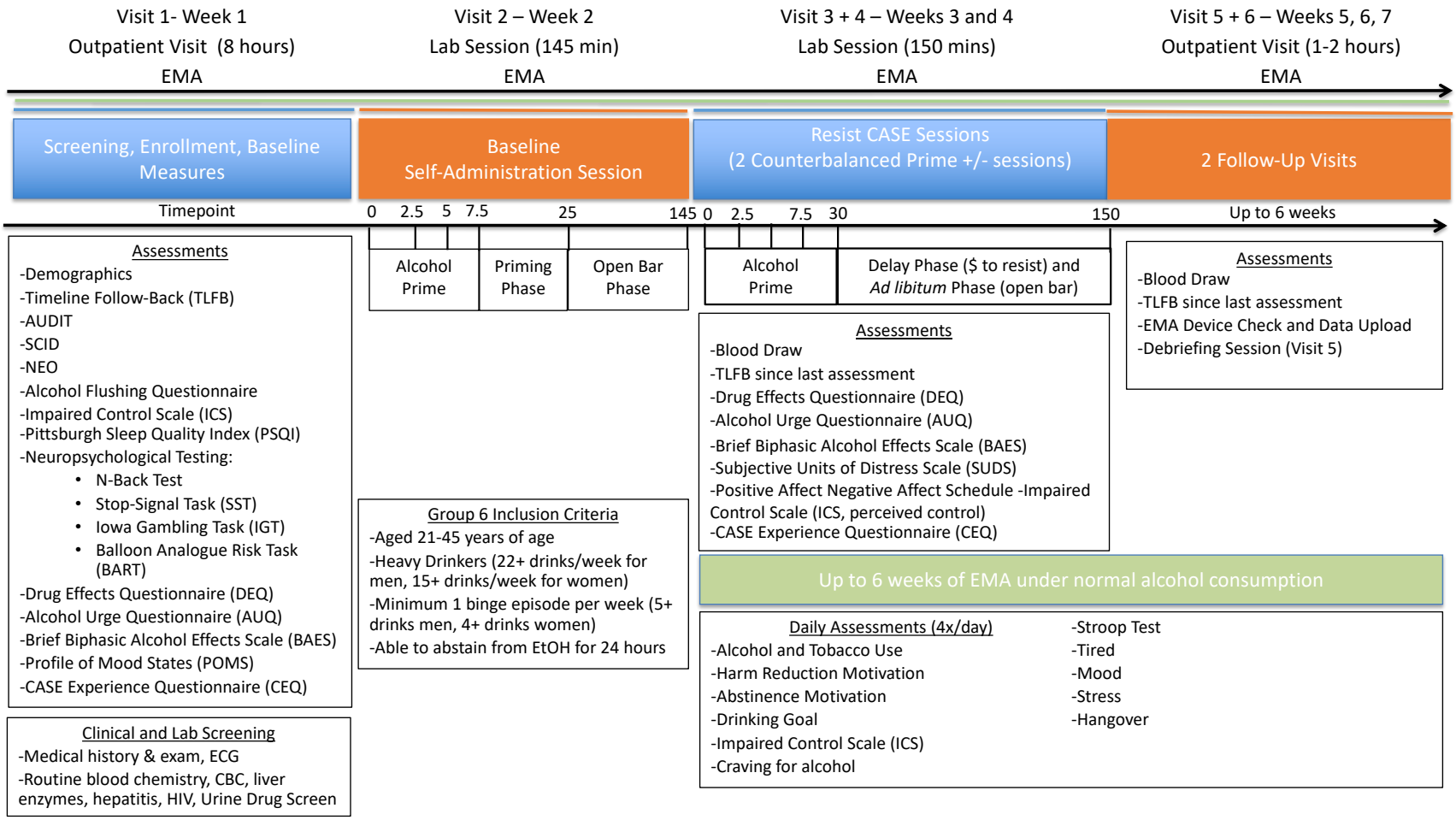

Figure 1. Overall Study Timeline

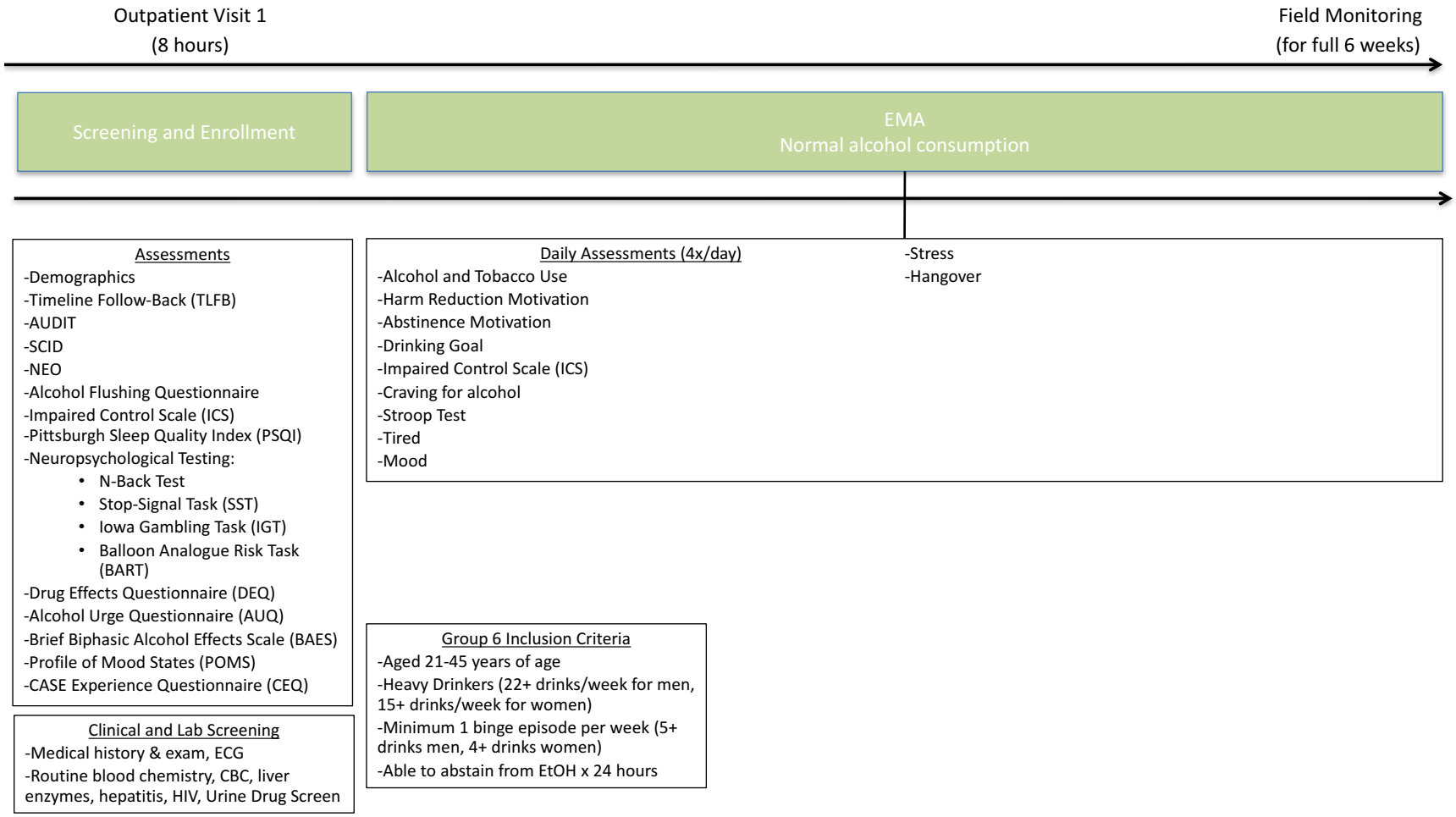

Figure 2. EMA Study Timeline

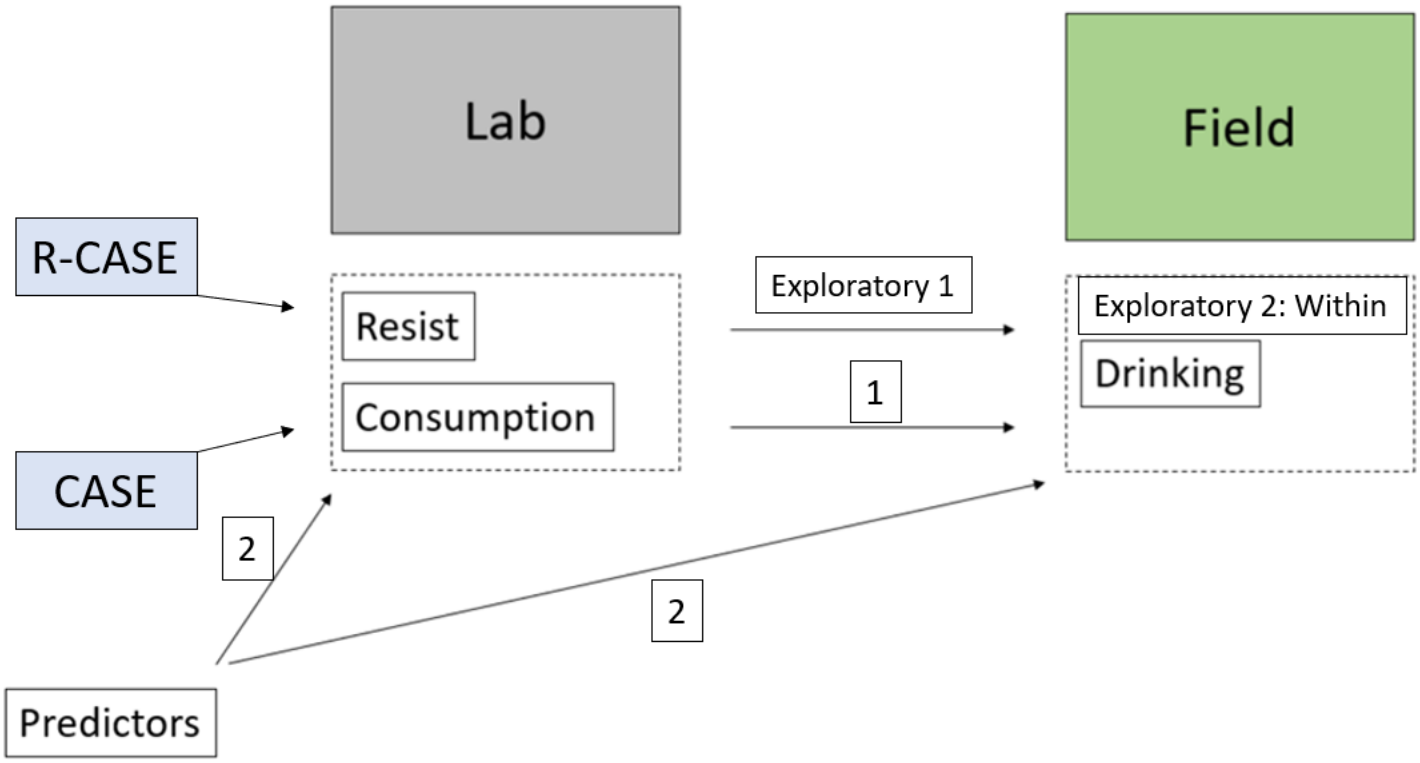

Figure 3. Specific Aims

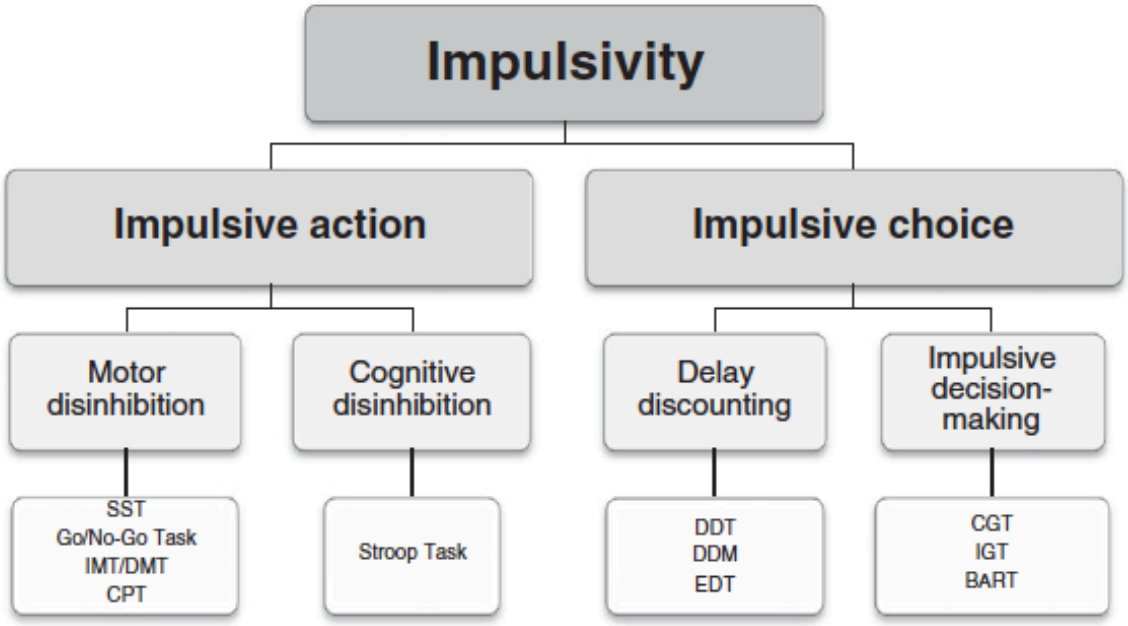

Figure 4. Neurocognitive Conceptualization of Impulsivity (Stevens et al., 2014).
Note. Reprinted from Journal of Substance Abuse Treatment, 47/1, Stevens, L., Verdejo-Garcia, A. E., Goudriaan, H. R., Geert Dom, W., Impulsivity as a vulnerability factor for poor addiction treatment outcomes: A review of neurocognitive findings among individuals with substance use disorders, 58-72, 2014, with permission from Elsevier.

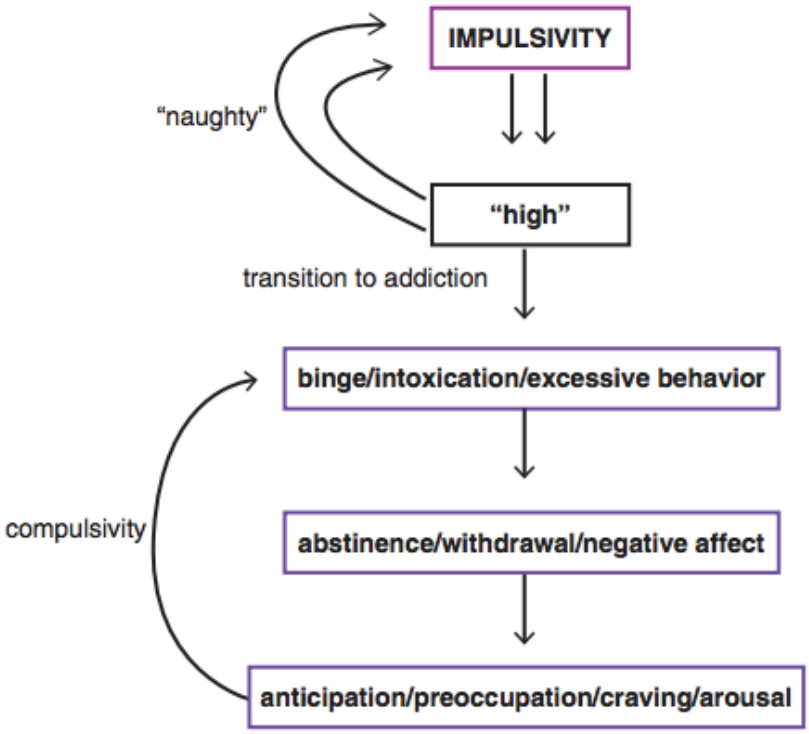

Figure 14-5. Shifting from impulsivity to compulsivity. Drug addiction provides a good example of the shift from impulsivity to compulsivity that comes with migration from ventral to dorsal circuits. The impulse to take a drug initially leads to great pleasure and satisfaction (a "high"). If this happens infrequently, the behavior may be a bit "naughty" but will not necessarily progress to compulsivity. With chronic substance use, compulsivity may develop as an individual's drive turns from seeking pleasure to seeking relief from distressing symptoms of withdrawal and anticipation of obtaining the drug.

Figure 5. Hypothesized Relationship Between Impulsivity and Compulsivity (Stahl, 2013).

Note. Reprinted from Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications, Edition 4, 2013, with permission *pending* from Cambridge University Press.

Seq	Name	Text	Answer1	Answer2	Answer3	Answer4	Answer5
		Brief Reminder of Definition of Standard Drink					
1	Drinking Goal	At the current time would you rather maintain your normal drinking pattern, cut down on your drinking, or avoid drinking altogether?	Maintain normal drinking pattern	Cut down on drinking	Avoid drinking altogether		
2	Motivation 1	How motivated are you to cut down on your usual alcohol consumption in the next 24 hours?	Not at all	A little	Moderately	Quite a bit	Extremely
3	Motivation 2	How motivated are you to stop drinking altogether in the next 24 hours?	Not at all	A little	Moderately	Quite a bit	Extremely
4	Consumption Quantity	Since your last assessment how many drinks have you had?	No drinks	1 drink	2 to 3 drinks	4 drinks	5 or more drinks
5	Consumption Timing	How long ago was your last drink?	I am drinking now	Less than 1 hour ago	1-2 hours ago	2-3 hours ago	More than 3 hours ago
6	Alcohol Craving	I crave a drink right now.	Not at all	A little	Moderately	Quite a bit	Extremely
7	Perceived Control 1	At the current time I would start to drink, even after deciding not to.	No	Yes			
8	Perceived Control 2	At the current time I would be able to stop drinking after one or two drinks.	No	Yes			
9	Mood 1 – Bored	Within the past hour, I felt bored.	No	Yes			
10	Mood 2 - Sad	Within the past hour, I felt sad.	No	Yes			
11	Mood 3 – Angry	Within the past hour, I felt angry or frustrated.	No	Yes			
12	Mood 4 – Anxiety	Within the past hour, I felt worried, anxious or tense.	No	Yes			
13	Mood 5 - Good Mood	Within the past hour, I was in a good mood.	No	Yes			
14	Stress	How stressed do you feel right now?	Not at all	A little	Moderately	Quite a bit	Extremely
15	Tired	How tired do you feel right now?	Not at all	A little	Moderately	Quite a bit	Extremely
16	Hangover	How hungover do you currently feel?	Not at all	A little	Moderately	Quite a bit	Extremely
17	Smoking	Since your last assessment, how many cigarettes have you smoked?	No cigarettes	1 cigarette	2 cigarettes	3 cigarettes	4+ cigarettes

18	Cigarette Craving	I crave a cigarette right now.	Not at all	A little	Moderately	Quite a bit	Extremely
19	Interruption	When you were doing this task, on how many occasions were you interrupted, for example by the telephone ringing or by somebody trying to talk to you?	No times	1 time	2 times	3 times	4+ times

Figure 6. EMA Questions

At the current time:

I feel bored.	Not at all	A little	Moderately	Quite a bit	Extremely
I feel sad.	Not at all	A little	Moderately	Quite a bit	Extremely
I feel angry or frustrated.	Not at all	A little	Moderately	Quite a bit	Extremely
I feel worried, anxious or tense.	Not at all	A little	Moderately	Quite a bit	Extremely
I am in a good mood.	Not at all	A little	Moderately	Quite a bit	Extremely

Figure 7. Laboratory Mood Questions

Part 1 is rated using a five-point scale: (1) Never, (2) Rarely, (3) Sometimes, (4) Often, (5) Always. Part 2 uses the same five-point scale but also has a sixth category "Does Not Apply". Part 3 uses a different five-point scale: (1) Strongly Agree, (2) Agree, (3) Undecided, (4) Disagree, (5) Strongly Disagree.

PART 1: Attempted Control
[a]*During the last 6 months*

(1) I tried to limit the amount I drank
(2) I tried to resist the opportunity to start drinking
(3) I tried to slow down my drinking
(4) I tried to cut down my drinking (i.e. drink less)
(5) I tried to stop drinking for a period of time

PART 2: Failed Control
[a]*During the last 6 months*

(1) I found it difficult to limit the amount I drank
(2) I started drinking even after deciding not to
(3) Even when I intended having only one or two drinks, I ended up having many more
(4) I was able to cut down my drinking (i.e. drink less) when I wanted to
(5) I started drinking at times when I knew it would cause me problems (i.e. problems at work, with family/friends or with the police, etc.)
(6) I was able to stop drinking easily after one or two drinks
(7) I was able to stop drinking before becoming completely drunk
(8) I had an irresistible urge to continue drinking once I started
(9) I found it difficult to resist drinking, even for a single day
(10) I was able to slow down my drinking when I wanted to

PART 3: Perceived Control
What do you think would happen now?

(1) I would find it difficult to limit the amount I drink
(2) I would start to drink even after deciding not to
(3) Even if I intended having only one or two drinks, I would end up having many more
(4) I could cut down my drinking (i.e. drink less) if I wanted to
(5) I would start drinking at times when I knew it would cause me problems (e.g. problems at work, with family/friends, or with the police, etc.)

Figure 8. Impaired Control Scale (ICS)

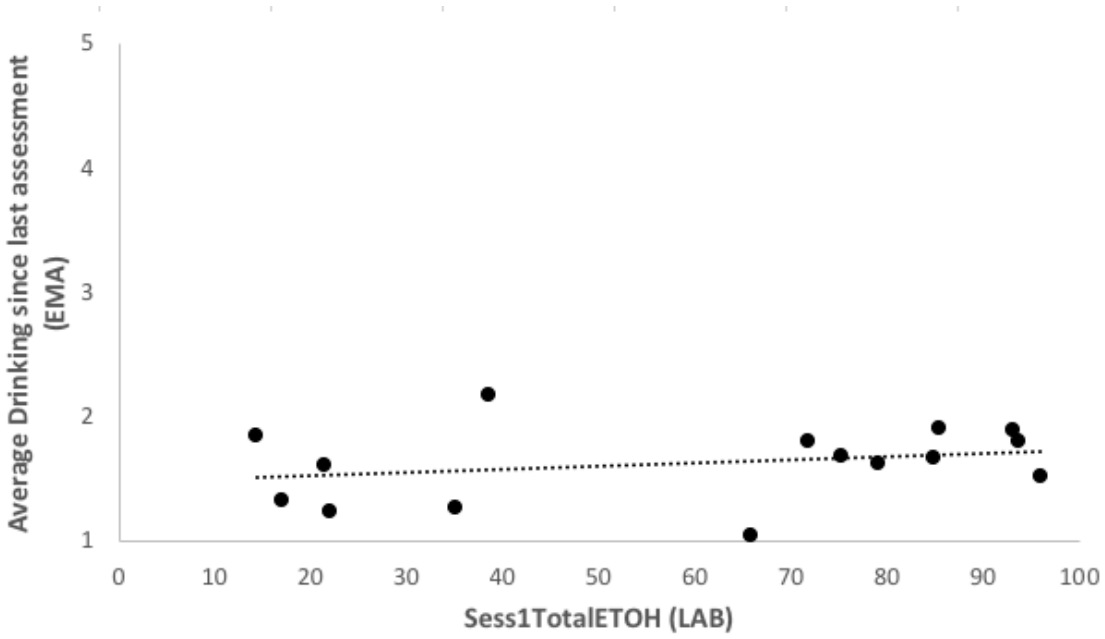

Figure 9. EMA drinking by Session 1 Total Ethanol Consumed

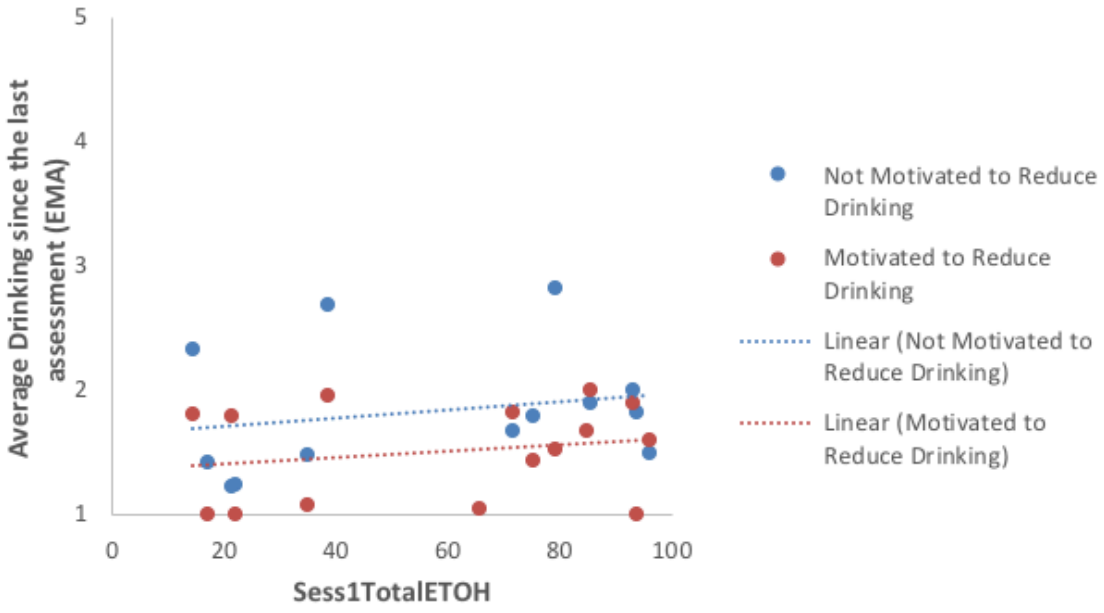

Figure 10. EMA drinking by Session 1 Total Ethanol Consumed by Motivation

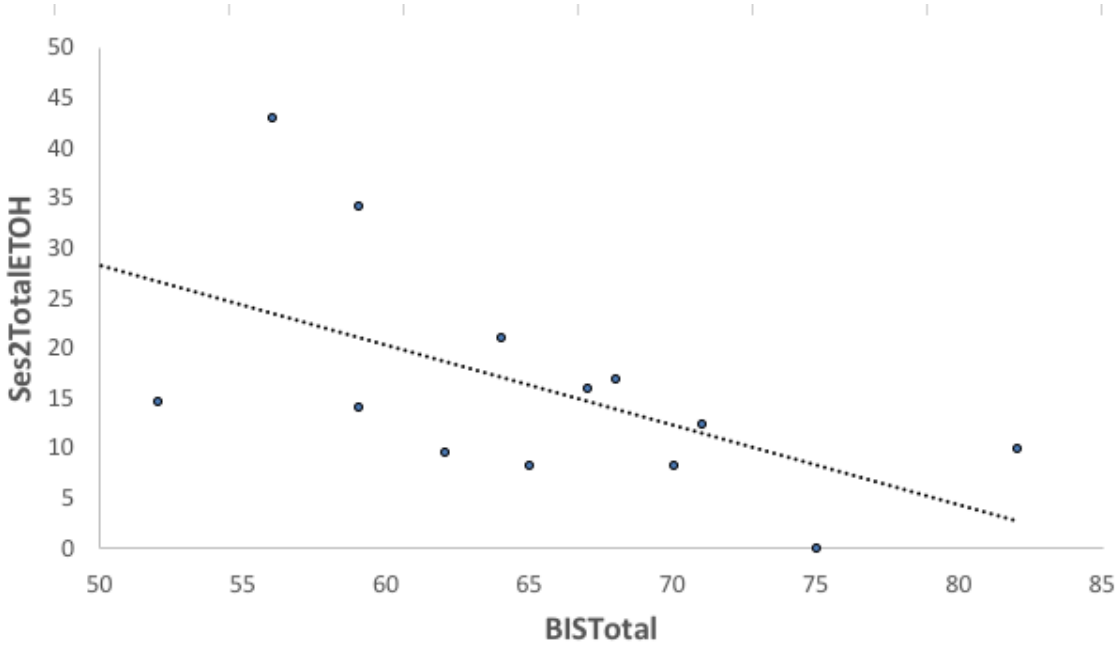

Figure 11. Session 2 Total ETHOH consumed by Barratt Impulsivity Scale Total

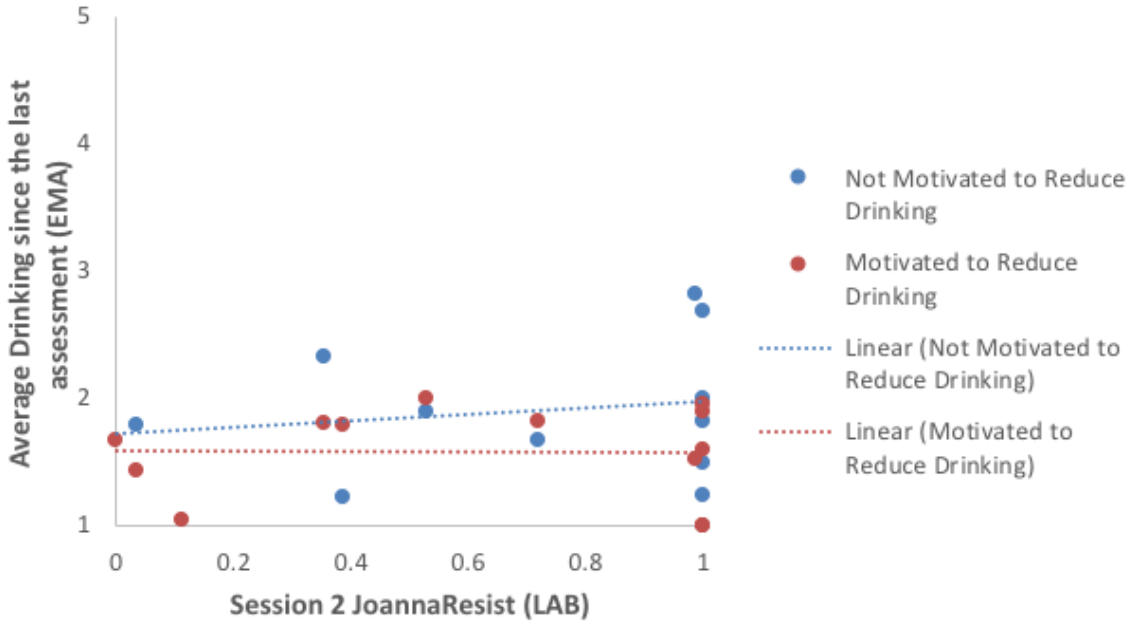

Figure 12. EMA drinking by Resist in Proportion of Minutes by Motivation

APPENDIX A: RECRUITMENT ADVERTISEMENTS

For NIAAA IRP Website:
Developing a Human Laboratory Model for Alcohol Self-Administration (Protocol 08-AA-0178)
This research study seeks to develop a human laboratory model for studying alcohol dependence and treatment by using a procedure for self-administering alcohol intravenously (through a vein).
Research participation includes 4-5 outpatient study visits consisting of alcohol self-administration, bloods draws, filling out questionnaires, and structured interviews.
The study is enrolling 21-60 year-old male and female social drinkers, binge drinkers. and heavy drinkers. You may be eligible if you have no psychiatric disorders and are free of certain medical conditions. You may not be eligible if you are pregnant or breastfeeding, have a history of drug and alcohol abuse, regularly use tobacco, or take any medications that would interfere with the study or make it unsafe for you. Free transportation is provided to and from the study site at the NIH Clinical Center in Bethesda, Maryland. Some study visits require you to stay overnight at the Clinical Center may take up to 10 hours. There is no cost to participate and compensation up to $1000 may be provided.
For more details, call (301) XXX-XXXX or email: NIAAASHPResearch@mail.nih.gov.

For Craigslist, Listservs at NIH (including OPR) and Local Universities:
Do you drink Alcohol? Drink daily or almost daily? Are you between the ages of 21 and 60?
We are seeking men and women for a study of alcohol self-administration behavior in a human research laboratory setting. Volunteers should be healthy and drug-free, and not seeking treatment for alcohol-related problems.
Research participation includes 4-5 outpatient study visits at the National Institutes of Health Clinical Center in Bethesda MD. Study visits consist of alcohol self-administration, blood draws, and filling out questionnaires. Some study visits require you to stay overnight at the Clinical Center. There is no cost to participate and compensation up to $1000 may be provided.
For more details, call (301) -XXX-XXXX or email: NIAAASHPResearch@mail.nih.gov.
Online: visit clinicaltrials.gov. Refer to Study 08-AA-0178.

Facebook/Twitter, ResearchMatch, and CC News/NIH Record:
Note: url for study is: https://clinicalstudies.info.nih.gov/cgi/detail.cgi?A_2008-AA-0178.html

Clinical Center Facebook (links to study-specific webpage on the OPR recruitment website, http://www.cc.nih.gov/recruit/protocols.html or CC Search the Studies)

Researchers at the National Institutes of Health (NIH) seek volunteers, 21 - 60 year-old, who drink daily or almost daily, to participate in a study of alcohol self-administration behavior in a human research laboratory setting. There is no cost to participate and compensation up to $1000 may be provided. Learn more at: (*url here*)

Clinical Center Twitter (links to study page on clinicaltrials.gov OR NIAAA IRP website)
21 – 60 year-old volunteers who drink daily or almost daily needed for study @NIHClinicalCntr: (*url here*)

CC News/NIH Record
NIAAA invites volunteers, 21 - 60 years of age, who drink daily or almost daily, to participate in a study of alcohol self-administration in a human research laboratory setting. Volunteers should be healthy and drug-free, and not seeking treatment for alcohol-related problems. Research participation includes 4-5 outpatient study visits which consist of alcohol self-administration, blood draws, and filling out questionnaires. Some study visits require you to stay overnight at the Clinical Center. Compensation up to $1000 may be provided. For more information, call 301- XXX-XXXX, or email: NIAAASHPResearch@mail.nih.gov, or visit clinicalstudies.info.nih.gov. Refer to 08-AA-0178.

NEWSPAPER ADVERTISEMENTS:

Do You Drink Alcohol Daily or Almost Daily?

NIAAA invites volunteers, 21 - 60 years of age, who drink daily or almost daily, to participate in a study to examine alcohol self-administration in a human research laboratory setting.

Research participation includes 4-5study visits which consist of alcohol self-administration, blood draws, and filling out questionnaires. Some study visits require you to stay overnight at the Clinical Center.

Volunteers should be healthy and drug-free, and not seeking treatment for alcohol-related problems.

Compensation up to $1000 may be provided.

For more information, call 301-XXX-XXXX or visit clinicaltrials.gov. Refer to 08-AA-0178.

NIH National Institute on Alcohol Abuse and Alcoholism

Do You Drink Alcohol?

Research study evaluating the choices people make about money and alcohol and how this relates to drinking.

Volunteers should be healthy, drug-free, NOT seeking treatment for alcohol problems, and NOT trying to cut down on drinking.

Research participation includes 4-5study visits with IV alcohol consumption, blood draws, and filling out questionnaires. Some study visits require you to stay overnight at the Clinical Center.

Compensation up to $1000

For more information, call 301-XXX-XXXX or visit clinicaltrails.gov. Refer to 08-AA-0178

NIH National Institute on Alcohol Abuse and Alcoholism

Researchers at the National Institutes of Health (NIH) seek volunteers, 21 – 60 years old, who drink daily or almost daily, to participate in a study to examine alcohol self-administration in a human research laboratory setting.
Compensation up to $1000 may be provided.

Study information:

- Participation involves 4-5 study visits at the NIH Clinical Center in Bethesda, MD. Some study visits require you to stay overnight at the Clinical Center.
- Screening with a medical history, physical exam, blood tests, and questionnaires
- Volunteers should be healthy and drug-free, and not seeking treatment for alcohol-related problems.

Location: The NIH Clinical Center, America's research hospital, is located on the Metro red line (Medical Center stop) in Bethesda, Maryland.

For more information, please call:

NIAAA HP Section: 301-XXX-XXXX
TTY: 1-866-411-1010

Online: clinicaltrials.gov

Refer to study 08-AA-0178

NIH National Institute on Alcohol Abuse and Alcoholism

NIH...*Turning Discovery Into Health*®

Volunteer NIAAA 301-XXX-XXXX

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Do You Drink Alcohol?

A study at the NIH is recruiting volunteers to examine alcohol self-administration in a human research laboratory setting.

Volunteers Needed

Compensation up to $1000 May be Provided

Must Be:

- 21 – 60 Years of Age
- Healthy and Drug-free
- Drink Daily or Almost Daily
- Not Seeking Treatment for Alcohol-Related Problems

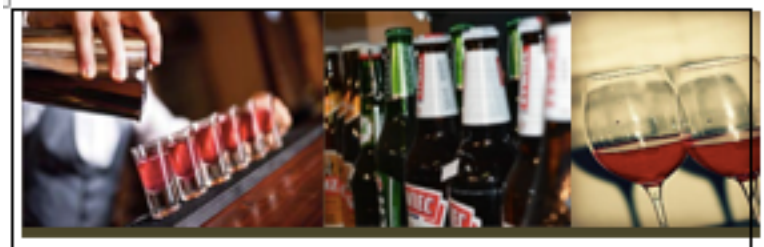
Includes 4 – 5 Study Visits

Please call 301-XXX-XXXX
Visit https://clinicaltrials.gov

Refer to study # 08-AA-0178

NIH National Institute on Alcohol Abuse and Alcoholism

Volunteer NIAAA 301-XXX-XXXX



DO YOU DRINK ALCOHOL OFTEN?

WE NEED YOU FOR A RESEARCH STUDY IF YOU:

- Use Alcohol daily or almost daily
- Are healthy and drug-free
- Are NOT seeking treatment

Participants may earn up to $1000

- Participation may include 4–5 study visits
- Studies take place in Bethesda, MD
- This is a study examining control over drinking.

Call: **301-XXX-XXXX**
Email:
NIAAASHPResearch@nih.gov
Visit clinicaltrials.gov
Refer to 08-AA-0178

NIH National Institute on Alcohol Abuse and Alcoholism

Do you drink alcohol? Are you 21-60 years old?

Our study investigates the alcohol self-administration in a human research laboratory setting. We are recruiting men and women who drink daily or almost daily.

- Participants will have 4-5 study visits. Some study visits require you to stay overnight at the Clinical Center.
- Study visits consist of IV alcohol administration, blood draws, and filling out questionnaires, and more.
- Participants may be compensated up to $1000.
- Studies take place at the National Institutes of Health Clinical Center in Bethesda, MD.

Call today for a confidential screening.

Contact us:
(301) XXX-XXXX
NIAAASHPResearch@mail.nih.gov

NIH National Institute on Alcohol Abuse and Alcoholism

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