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INDIVIDUAL DIFFERENCES IN ESCALATION OF TOBACCO USE: IMPULSIVITY AND ALCOHOL USE

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INDIVIDUAL DIFFERENCES IN ESCALATION OF TOBACCO USE: IMPULSIVITY AND ALCOHOL USE

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By
Dustin Clark Lee

Lexington, Kentucky

Director: Dr. Thomas H. Kelly, Professor of Behavioral Science, Psychology and Psychiatry

Lexington, Kentucky

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ABSTRACT OF DISSERTATION

INDIVIDUAL DIFFERENCES IN ESCALATION OF TOBACCO USE:
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Like adolescents, young adults are at risk of initiating tobacco use and escalating to daily use and tobacco dependence. However, not every young adult who uses cigarettes intermittently becomes tobacco dependent, and the time-course of those who transition to daily use varies widely. Individual differences likely contribute to the variability observed in patterns of tobacco use. This dissertation uses a multi-modal research approach to examine dimensions of impulsivity and alcohol use that are associated with vulnerability for escalation of cigarette smoking, and whether alcohol's effects on behavioral disinhibition impact cigarette consumption. Study 1 investigated the associations between dimensions of trait impulsivity, alcohol use, and smoking behavior in a cross-sectional sample of young adults who varied in frequency of cigarette smoking. Study 2 expanded on the results of Study 1 by examining the separate and combined effects of impulsivity and alcohol use on escalation of tobacco use in a longitudinal study of young adults in their first three years of college to determine whether alcohol use and dimensions of impulsivity influenced trajectories of smoking behavior, and whether alcohol use and behavioral impulsivity changed across time as a function of tobacco use trajectories. Study 3 utilized a randomized, within-subject, placebo controlled design to examine whether alcohol-induced impairments in behavioral inhibition mediated the relationship between acute alcohol administration and ad-libitum cigarette consumption. Results from studies 1 and 2 indicated that alcohol use was associated with smoking frequency, and that dimensions of impulsivity (i.e. sensation seeking, lack of premeditation, and urgency) differentiated smoking groups. Study 3 found that acute alcohol increased smoking behavior, but alcohol impairment of inhibitory control did not mediate the relationship between alcohol and smoking consumption. Taken together, the results of these studies demonstrate that alcohol use and impulsivity play a significant role in tobacco use escalation,

though more research is needed to determine the mechanism(s) that drive alcohol-induced increases in cigarette consumption.

KEYWORDS: Tobacco, Alcohol, Impulsivity, Young Adults, Escalation

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INDIVIDUAL DIFFERENCES IN ESCALATION OF TOBACCO USE: IMPULSIVITY AND ALCOHOL USE

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Chapter One: Introduction

Background

Tobacco use remains prevalent in the United States, with an estimated 26.5% of Americans (68.2 million individuals) age 12 and older reporting current tobacco use in 2011 [National Survey on Drug Use and Health (NSDUH) 2012]. Tobacco-related illnesses are one of the leading and most costly causes of preventable illness and death in the United States; each year an estimated 443,000 tobacco-related deaths occur and $96 billion in direct health-care expenditures are attributable to tobacco-related illnesses [Center for Disease Control and Prevention (CDC), 2008]. Among current tobacco users, cigarette smoking is the most frequently reported route of administration, with 56.8 million individuals reporting current (past month) cigarette smoking (NSDUH, 2012). Of those who attempt to quit smoking, only 3 to 5% remain abstinent after 12 months without some form of treatment (Fiore, 2008; Hughes, Keely, & Naud, 2004). Treatment has been effective in decreasing the frequency of relapse rates over untreated quit attempts, but the long-term effectiveness of treatment varies widely based upon the method of treatment and characteristics of the population, and smoking relapse rates following treatment still remain high overall (Etter & Stapleton, 2006; Fiore, 2008).

Since the treatment of tobacco dependence has limited efficacy, development of screening and prevention efforts for non-users and escalating smokers remain integral for public health research aimed at reducing the overall burden of cigarette smoking. Prevention efforts have traditionally been directed

toward adolescents, since adolescence is a critical time period for risk of tobacco initiation and escalation of use (Backinger, Fagan, Matthews, & Grana, 2003; CDC, 1994). However, young adults have also been identified as an age group that is at risk for escalating tobacco use patterns. In 2011, young adults reported the highest rate of current tobacco use of any age group (39.5% among 18-25 year olds compared to 10.0% of youths aged 12-17 and 26.3% of adults aged 26 or older), and those 18 years or older accounted for nearly half of individuals who reported smoking initiation (approximately 46% of 2.4 million persons; NSDUH, 2012). Additional studies have reported that up to 25% of smokers first initiated smoking after turning age 18 (Everett et al., 1999; Foldes et al., 2010), and that approximately 28% of college students who smoke tobacco intermittently escalate to daily tobacco use at age 19 or older (Wechsler, Rigotti, Gledhill-Hoyt, & Lee, 1998). Young adults are also targeted by the tobacco industry for promotional campaigns aimed at increasing tobacco use prevalence in this age group, with exposure to tobacco-related advertisements and promotional materials placing them at further risk for initiation of smoking (Ling & Glantz, 2002; Rigotti, Moran, & Wechsler, 2005; U.S. Department of Health & Human Services, 2012).

Longitudinal research has further demonstrated that trajectories of cigarette smoking are heterogeneous, and that initiation and escalation of use occurs in both adolescence and in young adulthood (D. Brook et al., 2008; J. Brook, Ning, & Brook, 2006; Caldeira et al., 2012; Chassin, Presson, Pitts, & Sherman, 2000). In a longitudinal trajectory analysis, Chassin et al. (2000) found

that approximately 843 individuals out of a sample of 2,711 smokers were classified as “early stable smokers,” consisting of individuals who initiated early in adolescence and were daily smokers by the age of 15, while 1,108 individuals were classified as “late stable smokers,” which consisted of a transition to weekly smoking at age 18 or older. J. Brook et al. (2006) found that 25% of participants in a sample of 451 were classified as “early-starting continuous smokers” who reported smoking regularly from age 14, whereas 18.4% were classified as “late-starting smokers,” who did not initiate smoking until after the age of 18, then escalated to daily use by the age of 26. Similarly, D. Brook et al. (2008) found that 16.5% of participants in a sample of 746 were classified as “heavy/continuous smokers,” whereas 20.2% were classified as “late starters,” characterized by starting smoking in later adolescence and then increasing to stable daily patterns of tobacco use by the late twenties. No gender differences were observed between groups. Finally, Caldeira et al. (2012) examined trajectories of cigarette smoking in college students in a four-year study and found similar rates of 8.3% of college students in a sample of 1,253 in both “high-stable smokers” (those reporting smoking prior to college, and maintaining a similar pattern of use throughout the study), and “low-increasing” smokers, [initiation of use during the first year of college, followed by escalation of use to non-daily smoking, (approximately 15 days out of the month), by the fourth year of college]. Each study demonstrated that a significant proportion of smokers developed regular smoking patterns after the age of 18. With few exceptions, gender was equally distributed across trajectory groups. Taken together, these

detailed analyses of the trajectories of tobacco use demonstrate that both adolescents and young adults are at risk for initiating and transitioning into regular patterns of tobacco use, which underscores the need for screening and prevention efforts directed at both adolescents *and* young adults in order to decrease the prevalence of heavy tobacco use.

It is important to note that not every individual who initiates cigarette smoking becomes tobacco dependent. Approximately a third to a half of individuals who try cigarettes become daily smokers (Henningfield, Moolchan, & Zeller, 2003), and intermittent, or non-daily smoking has become more prevalent in adult cigarette smokers (Schane, Glantz, & Ling, 2009; Shiffman, 2009b). The timeline and prevalence of escalation to daily tobacco use is not clear, with some research indicating that non-daily tobacco users generally escalate to daily use within two years of initiation, while others show that some smokers remain intermittent, less than daily users for longer periods of time, sometimes indefinitely (e.g. Evans et al., 1992; Hassmiller, Warner, Mendez, Levy, & Romano, 2003; Levy, Biener, & Rigotti, 2009; Shiffman, 2009b; Schane et al., 2009). The relationship between risk factors and transitioning patterns of tobacco use in young adults is still uncertain, and it is likely that multiple factors may make unique contributions to initiation and escalation of use. It is critical to understand potential predictors and associational factors related to transitions in tobacco use during this developmental period of emerging adulthood. Thus, the broad aim of this dissertation research is to examine patterns of tobacco use in

order to determine how individual difference variables may influence vulnerability to tobacco initiation and escalation in young adults.

Alcohol Consumption and Smoking

Alcohol consumption is a known risk factor for cigarette smoking and problematic smoking behavior. Among young adults aged 18 to 25, nearly 80% of people who reported smoking cigarettes in the past month also reported drinking alcohol, compared to 53% of people who did not report smoking cigarettes (NSDUH, Table 6.26B, 2012). Among past-month cigarette smokers, over 60% reported binge drinking (i.e., five or more drinks per occasion on at least one day in the past 30 days) and 23% reported heavy drinking (i.e., five or more drinks on same occasion on each of 5 or more days in the past 30 days), compared to 29% and 7%, respectively, among non-smokers. Prevalence of cigarette smoking follows an increasing trend based on young adults' level of alcohol use, such that lowest rates of cigarette use are reported among alcohol non-users (22.7%), followed by non-binge users (32.3%), past-month binge users (53.8%), and finally heavy alcohol users (73.4%) (NSDUH, Table 6.30B, 2012).

Longitudinal and cross-sectional studies have further identified alcohol use as a risk factor that is associated with smoking initiation in college students (Reed, Wang, Shillington, Clapp, & Lange, 2007; Reed, McCabe, Lange, Clapp, & Shillington, 2010), and escalation from non-smoking to non-daily patterns of tobacco use in early adulthood (White, Bray, Fleming, & Catalano, 2009). Young

adult non-daily and daily smokers frequently report using alcohol and tobacco concurrently (Dierker et al., 2006; Harrison, Desai, & McKee, 2008; Jackson, Sher, & Schulenberg, 2005; Shiffman, Dunbar, Scholl, & Tindle, 2012; Weitzman & Chen, 2005), and alcohol use increases the reinforcing and pleasurable effects of tobacco among non-daily smokers (McKee, Hinson, Rounsaville, & Petrelli, 2004). Moreover, among adult smokers, those who report co-occurring alcohol and smoking use more cigarettes per drinking episode and are less likely to remain abstinent following a quit attempt (Kahler, Spillane, & Metrik, 2010).

Laboratory studies have generally confirmed the relationship between alcohol and smoking by showing that acute alcohol increases smoking behavior, as measured by cigarette self-administration (Barrett, Campbell, Roach, Stewart, & Darredeau, 2013; King, McNamara, Conrad, & Cao, 2009; McKee, Harrison, & Shi, 2010; Mintz, Boyd, Rose, Charuvastra, & Jarvik, 1985). However, this does not appear to result from a direct pharmacological interaction between nicotine and alcohol alone, since studies have shown that: 1) alcohol does not increase intranasal nicotine self-administration (Perkins, Fonte, Blakesley-Ball, Stolinski, & Wilson, 2005), and 2) increases in both denicotinized and nicotinized cigarette self-administration occur at comparable rates following alcohol consumption in non-daily smokers (Barrett et al., 2013; King et al., 2009). This evidence suggests that other mechanisms drive alcohol-induced escalation of cigarette smoking.

Taken together, the current body of literature has demonstrated that alcohol is a potent risk factor for acute and long-term increases in cigarette

smoking behavior. Identifying the underlying mechanism(s) responsible for alcohol-induced increases in cigarette smoking is important in order to understand the effect of alcohol on cigarette smoking, which would aid in prevention and treatment efforts aimed at decreasing concurrent use of both drugs. However, few studies to date have examined the effects of alcohol while controlling for other risk factors associated with smoking, and as such, the independent causal association between alcohol and smoking remains uncertain. One risk factor in particular, impulsivity, obscures the independent association between alcohol and smoking because it has been associated with increased risk for initiation and escalation of both alcohol and tobacco, and is, in turn, modified by alcohol and nicotine (e.g. Carton, Jouvent, & Widlocher, 1994; Granö, Virtanen, Vahtera, Elovainio, & Kivimäki, 2004; Lynam & Miller, 2004; Miller, Flory, Lynam, & Leukefeld, 2003; Moallem & Ray, 2012; Mitchell, 1999; 2004; Smith et al., 2007; VanderVeen, Cohen, & Watson, 2013).

Impulsivity and Smoking

Individual differences in impulsivity have been associated with problematic tobacco use and dependence. Impulsivity is a multifaceted personality construct (e.g. Depue & Collins, 1999; de Wit, 2009; Evenden, 1999) that has been quantified using self-report trait measures, (e.g. Whiteside & Lynam, 2001) and laboratory-based behavioral inhibition tasks (e.g. Bickel, Odum, & Madden, 1999; Logan & Schachar, 1997). However, studies have found minimal correlations between self-report trait impulsivity and behavioral measures of inhibition (e.g.

Reynolds, Ortengren, Richards, & de Wit, 2006) suggesting that self-report and behavioral measures are not isomorphic. In a recent review, Dick and colleagues, (2010) suggested that self-report trait measures of impulsivity refer to stable differences in how individuals perceive the world and behave in accordance with those perceptions, whereas behavioral measures assess relatively specific cognitive processes. Thus, it is possible that self-report trait and behavioral measures of impulsivity inform the trajectories of cigarette use independently.

Self-report trait measures of the multifaceted construct of impulsivity have identified multiple dimensions, such as inhibition, sensation seeking, risk-taking, novelty seeking, boredom susceptibility, and unorderliness (Depue & Collins, 1999). While there is no consensus as to the best self-report approach for assessing the trait of impulsivity, the UPPS (Whiteside & Lynam, 2001) has become widely used in the past decade. Whiteside and Lynam (2001) used a factor analytic approach to examine several commonly used self-report measures of impulsivity (e.g., Cloninger, Przybeck, & Svrakic, 1991; Dickman, 1990; Eysenck & Eysenck, 1985; Patton, Stanford, & Barratt, 1995; Tellegen, 1982; Zuckerman, 1994), and identified 4 factors: (1) ***U****rgency*, which refers to the tendency to experience strong impulses while under a negative mood; (2) (Lack of) ***P****remeditation*, which refers to the tendency to think about the consequences of an act beforehand; (3) (Lack of) ***P****erseverance*, which refers to the ability to remain focused on projects and resisting distraction; and (4) ***S****ensation Seeking*, which refers to the tendency to enjoy exciting and risky

activities. The UPPS model was later updated to include positive urgency (tendency to experience strong impulses in response to positive emotional stimuli (UPPS-P; Cyders & Smith, 2008). Results from confirmatory factor analyses testing this model support the distinctiveness of these traits over a unidimensional conceptualization of impulsivity (e.g., Magid & Colder, 2007; Smith et al., 2007) and highlight the importance of considering the contributions of multiple impulsivity-related dimensions when investigating the development of risky behaviors. The UPPS (and UPPS-P) has been used extensively to evaluate impulsive personality traits and risk-related behaviors such as drug-use, risky sexual behavior, and externalizing disorders (e.g. Cyders et al., 2010; Settles et al., 2012), and is considered among the best available tools for examining the relationship between key trait dimensions of impulsivity and risk-related behaviors.

Studies using the UPPS and other personality measures to examine individual differences in cigarette smoking have found a relationship between several dimensions of impulsivity and cigarette smoking. For instance, sensation seeking is associated with initiation of smoking (Lipkus, Barefoot, Williams, & Siegler, 1994; Perkins et al., 2008), initiation of daily smoking in adolescence (Spillane et al., 2012), current smoking levels (Flory & Manuck, 2009; Spillane, Smith, & Kahler, 2010), and positive dimensions of craving (craving the positive effects of nicotine; e.g., Doran, Cook, McChargue, & Spring, 2009).

Measures of inhibition (including lack of premeditation and lack of perseverance) are less frequently associated with tobacco initiation but there is

some evidence that non-planning impulsivity is associated with symptoms of tobacco dependence (Chase & Hogarth, 2011; Flory & Manuck, 2009), although this finding is not ubiquitous (Spillane et al., 2010; 2012). Hogarth (2011) found that non-planning impulsivity was unrelated to rates of cigarette seeking and smoking, and moderated the association between craving and smoking, suggesting that smoking is controlled by automaticity rather than by motivational aspects related to craving for those high in non-planning impulsivity. It is possible that the vulnerability for smoking among those high in disinhibition may be more related to cigarette availability than to symptoms associated with tobacco dependence (e.g. craving, withdrawal).

Conversely, the impulsivity dimension of urgency has been associated with tobacco dependence (e.g. Spillane et al., 2010), negative dimensions of tobacco craving (craving relief from the negative effects of tobacco deprivation; e.g., Billieux, Van der Linden, & Ceschi, 2007; Doran et al., 2009), and heightened expectancies for the negative reinforcing effects of smoking (Spillane et al., 2012).

Taken together, the preceding findings suggest that the impulsivity dimension of sensation seeking is closely associated with initiation and uptake of cigarette smoking, whereas disinhibition and urgency are more closely associated with the loss of control and development of tobacco dependence. Overall, these studies also give some insight into the relationship between dimensions of impulsivity and stages of cigarette smoking. However, given the broad use of 'impulsivity' and the cross-sectional nature of existing studies, more

research is needed to determine which dimensions of self-report trait impulsivity predict escalation of tobacco use.

In addition to self-report measures of impulsivity, behavioral tasks have been used in both preclinical and clinical studies to measure individual differences in behavioral inhibition and response to nicotine and cigarette smoking (e.g. Mitchell, 2004). Like self-report measures, behavioral tasks have also identified multiple dimensions of impulsivity. Broadly, behavioral measures of inhibition assess impulsive choice (i.e., delay discounting tasks), impulsive action (i.e., inhibitory control) and inattention; the first two dimensions, impulsive choice and impulsive action, have been associated with drug use (de Wit, 2009; Mitchell, 2004). It is also possible that performance on behavioral measures of inhibition can both predict drug use and change as a consequence of drug use (de Wit, 2009), so it is important to understand the causal relationship between behavioral inhibition and drug use.

Research using delay discounting tasks have found that current smokers discount rewards at a greater magnitude than non-smokers (Bickel et al., 1999; Heyman & Gibb, 2006; Mitchell, 1999; Reynolds & Fields, 2012), ex-smokers (Bickel et al., 1999) and non-dependent smokers (Heyman & Gibb, 2006; Reynolds & Fields, 2012). However, recent research has demonstrated that delay-discounting rates remain stable over a long period of time (Audrain-McGovern et al., 2009). Research using tasks of inhibitory control (e.g. stop-signal tasks) to measure individual differences in cigarette smokers are less frequent, though recent studies have found an association between increased

inhibitory errors on a stop signal task and both magnitude of tobacco dependence (Billieux et al., 2010) and personality dimensions of impulsivity (Fillmore, Ostling, Martin, & Kelly, 2009). Nonetheless, the causal relationship between cigarette use and behavioral inhibition remains speculative given the cross-sectional approaches used in the majority of these studies. Longitudinal studies are needed to determine whether decrements in behavioral inhibition predict, or are a consequence of increasing tobacco use.

Impulsivity, Alcohol Consumption, and Smoking

While alcohol use and impulsivity are both potential risk factors for cigarette smoking, they are not necessarily independent correlates of smoking behavior. The associations between impulsivity and cigarette smoking are also seen between impulsivity and alcohol use. For instance, sensation seeking and lack of premeditation are predictors of early onset of alcohol use, and sensation seeking has been identified as a predictor of higher alcohol use frequency (e.g., Lynam & Miller, 2004; Smith et al., 2007). In contrast, both lack of premeditation and negative urgency appear to be important predictors of alcohol abuse and dependence or problematic use (e.g., Fischer & Smith, 2008; Lynam & Miller, 2004; Magid & Colder, 2007; Smith et al., 2007). Less research has focused on the co-occurrence of smoking and alcohol consumption, but there is evidence that the co-use of both drugs is associated with heightened impulsivity. Specifically, heavy drinking smokers exhibit more inhibitory errors, greater delay discounting, and higher levels of trait disinhibition than those who use one

substance independent from the other (Moallem & Ray, 2012; VanderVeen et al., 2013). These findings emphasize the similarities between impulsivity dimensions and the developmental progression of both tobacco and alcohol use, and suggest that impulsivity could be a potential risk factor that accounts for increases in both alcohol consumption and cigarette smoking.

This association between impulsivity and alcohol is not unidirectional. Evidence also indicates that alcohol impacts behavioral inhibition, and that the behavioral effects of alcohol are independent of trait impulsivity. Multiple studies have demonstrated that inhibitory control on cued go/no-go and stop signal tasks is impaired following consumption of alcohol (e.g. Marczinski & Fillmore, 2003; Dougherty, Marsh-Richard, Hatzis, Nouvion, & Mathias, 2008). Alcohol increases the magnitude of acute impairments of inhibitory control at similar rates in those who differ in trait measures of impulsivity (Fillmore et al., 2009). Furthermore, the magnitude of alcohol impairment of inhibitory control predicts subsequent ad-libitum alcohol consumption (Weafer & Fillmore, 2008), suggesting that impaired inhibitory control may be a behavioral mechanism that is associated with escalation in drug use. However, no study to date has investigated the possibility that acute alcohol-induced decrements in inhibitory control may be associated with acute escalation of cigarette smoking.

These studies provide clear evidence that the effects of alcohol and impulsivity are bidirectional, raising questions about the independent influences of these two risk factors on cigarette smoking. It is clear that studies examining

the causal relationship between alcohol and smoking must also address the separate and combined effects of impulsivity.

Rationale

The aims of this dissertation research were to 1) determine the dimensions of impulsivity and characteristics of alcohol use that are associated with increases in cigarette smoking, and 2) determine if alcohol's impairment of behavioral inhibition mediates the relationship between acute alcohol administration and increases in cigarette smoking, in young adults. To accomplish these aims, I utilized a multi-modal approach with cross-sectional and longitudinal correlational designs, as well as a laboratory-based experimental design. The advantages of a correlational approach are that it allows for a broad observation of multiple potential risk factors (e.g., impulsivity and alcohol use) associated with tobacco escalation using large sample sizes and longitudinal data analytic techniques. However, the disadvantage to this approach is that it is observational in nature, and potential variables of interest cannot be directly manipulated. Using an experimental approach, while limited in terms of sample size and potential generalizability, allows for a closer inspection of potential mechanisms that may be related to concurrent alcohol and tobacco use by directly manipulating the variables of interest in order to establish a potential causal link between alcohol-induced decrements in behavioral inhibition and alcohol's effect on tobacco use.

Study 1 examined the independent contributions of alcohol consumption and UPPS-P impulsivity dimensions on current cigarette smoking status (i.e. non-smokers, non-daily smokers, daily smokers) in a sample of young adults prior to entering college. It was hypothesized that UPPS-P impulsivity (specifically sensation seeking and negative urgency), and alcohol use would be positively correlated with smoking frequency. In addition, when all variables were simultaneously controlled using a multinomial logistic regression model, it was hypothesized that sensation seeking would predict membership in the non-daily smoking group, while negative urgency would predict membership in daily smoking group, compared to both non-daily and non-smokers. Finally, consistent with prior literature demonstrating that tobacco users consume greater amounts of alcohol relative to non-smokers, it was hypothesized that greater alcohol use would predict membership in both smoking groups. This pattern of results would suggest that impulsivity and alcohol have independent associations with cigarette smoking status.

Study 2 expanded on the results of Study 1 by examining the trajectories of tobacco use across a three-year period in the same sample of college students in order to determine the independent effects of alcohol use and dimensions of impulsivity as risk factors for the emergence of problematic smoking behavior, and to determine if alcohol consumption and behavioral inhibition are altered as a consequence of escalating tobacco use. Based upon previous research, it was hypothesized that: 1) there would be four smoking groups defined by distinct patterns of tobacco use that emerged over the 3 year

time period, stable non-smokers, declining smokers (those who smoked prior to study entry and then quit over the course of the 3 year period), escalating smokers (those who increased cigarette use over time), and stable daily smokers; 2) frequent alcohol use would be associated with escalation of cigarette smoking; and 3) self-report trait measures of impulsivity would increase the probability of belonging to the escalating smoking trajectory, with higher scores on sensation seeking and urgency associated with escalation and heavy use, respectively. This pattern of results would suggest that impulsivity and alcohol have independent associations with the emergence of problematic smoking behavior.

Finally, Study 3 used a laboratory design to examine inhibitory control as a potential mechanism driving concurrent alcohol and tobacco use. Based on previous research, it was hypothesized that: 1) alcohol would increase ad-libitum cigarette smoking relative to placebo, 2) alcohol would also increase inhibition errors on a cued go/no-go task, and 3) the magnitude of alcohol-induced increases in inhibition errors would mediate the relationship between alcohol and increases in ad-libitum cigarette smoking behavior.

Implications

The research in this dissertation aims to broaden the field by examining factors that are associated with tobacco use initiation and escalation in young adult smokers. Identification of risk factors for escalation of tobacco use will help inform prevention and treatment interventions aimed at reducing the prevalence

of tobacco dependence, which in turn will reduce the societal burden of tobacco dependence, including healthcare costs and negative impact on quality of life. More specifically, the primary goal of this dissertation research is to examine the separate and combined roles of impulsivity and alcohol use on cigarette smoking in young adults, which is an age that has been linked to escalating patterns of tobacco use. Results from these studies will improve scientific knowledge by elucidating the relationship between individual differences in both impulsivity and characteristics of alcohol use and escalation of cigarette smoking, and evaluate a potential mechanism for alcohol-induced escalation of tobacco use. This knowledge will help inform screening and prevention efforts aimed at reducing the number of young adults who escalate to daily smoking.

Chapter Two: Study 1 – Cross-Sectional Analysis of Impulsivity and Alcohol Consumption as Risk Factors for Cigarette Smoking Status in Young Adults

Introduction

Young adults are at increased risk for smoking initiation and escalation to problematic patterns of use. Entry into college is a period of increased vulnerability to a variety of risk-related behaviors (e.g. Fromme, Corbin, & Kruse, 2008), including cigarette smoking. Up to 25% of college students begin smoking after turning eighteen (Everett et al., 1999), and approximately 28% of college students who smoke intermittently escalate to heavier patterns of use at the age of nineteen or older (Wechsler et al., 1998). However, it is important to note that not every young adult who initiates smoking transitions to daily use, (Henningfield et al., 2003) and intermittent, or non-daily smoking is prevalent in young adult cigarette smokers (Berg et al., 2012; Sutfin, Reboussin, McCoy, & Wolfson, 2009). Nevertheless, while the negative health-related effects of smoking are greatest in those who smoke daily, non-daily smokers are also at risk for increases in negative health-related effects (Caldeira et al., 2012; Schane, Ling, & Glantz, 2010) and have similar relapse rates as daily smokers during cessation attempts (Tindle & Shiffman, 2011). Thus, given the host of health problems associated with tobacco use—including non-daily smoking—it is critical to understand risk factors that predict these different patterns of tobacco use in young adults prior to transitioning to college to better guide prevention and treatment efforts.

As reviewed in the general introduction, there is substantial evidence that alcohol influences tobacco use and that dimensions of impulsivity influence consumption and problematic use patterns of both alcohol and cigarette use. However, the independent influence of these risk factors on smoking frequency is unknown. Therefore, the objective of this study was to investigate the associations between impulsivity, alcohol use, and smoking behavior in young adults who vary in frequency of cigarette smoking, in order to better understand risk factors associated with non-daily and daily tobacco use prior to entry into college. It was hypothesized that UPPS-P impulsivity (specifically sensation seeking and negative urgency), and alcohol use would be positively correlated with smoking frequency. In addition, when all variables were simultaneously entered into a multinomial logistic regression analysis, it was hypothesized that sensation seeking would predict membership in the non-daily smoking group, while negative urgency would predict membership in the daily smoking group, compared to both non-daily and non-smokers. Finally, consistent with prior literature demonstrating that tobacco users consume greater amounts of alcohol relative to non-smokers, it was hypothesized that greater alcohol use would predict membership in both smoking groups.

Method

Participants and Procedure

Participants were 525 young adults between the ages of 18-24 (52% female, mean age = 18.49), who were recruited from two successive freshmen

classes. During two consecutive academic years, all freshmen students in introductory psychology classes were invited to provide demographic information (i.e. sex, ethnicity, home state, and home country) in an in-class screening session for class credit. Inclusion criteria included: 1) between 18 and 24 years of age, 2) willingness to participate in the longitudinal study, and 3) in-state residence.

Each participant then completed one 2.5-hour session, which involved completion of computer-based questionnaires, behavioral tasks, and a structured interview assessing drug use. Participants completed a urine drug screening and a field sobriety test at the beginning of the session to ensure participants were not intoxicated at the time of the study. No participants were excluded from the study due to intoxication. All measures were administered by extensively trained research personnel, and questionnaires were administered via computer using the MediaLab software program. Participants were debriefed verbally by study personnel and in writing at the end of the study, and received course credit for taking part in the study. All procedures were reviewed and approved by the University of Kentucky Institutional Review Board.

Smoking Group Classification

Smoking group status was determined by using a Life History Calendar (LHC; Caspi, Moffitt, Thornton, & Freedman, 1996). The LHC is a retrospective method for collecting data on a wide range of life events and behaviors. Participants were asked to report on their substance use from age 13 to the time

of the interview. Each year was divided into three four-month intervals that correspond roughly to the two semesters of the school year and the summer. The most recent 4-month period at the time each participant completed the study was used to determine smoking group status.

Participants rated smoking frequency using a 0-5 scale: 0 = no smoking, 1 = once per month or less, 2 = once per week, 3 = two or three times per week, 4 = four or five times per week, and 5 = every day. Non-smokers (N = 399, 53% female) were defined as those who did not use cigarettes in the most recent period, and who did not report any prior attempts to quit smoking. Non-daily smokers (N = 60, 40% female) were those who reported using $\leq$ 5 days per week. Daily smokers (N = 41, 51 % female) reported smoking cigarettes daily. Twelve participants were daily smokers but had recently quit smoking in the most recent period and thirteen participants did not have tobacco use data from the most recent four-month period. These participants were excluded from the study, resulting in a final sample of 500.

Dependent Measures

Impulsivity

UPPS-P Impulsive Behaviors Scale (Lynam, Smith, Whiteside & Cyders, 2006; Whiteside & Lynam, 2001) is a 59-item inventory designed to measure five distinct personality pathways to impulsive behavior: negative urgency, (lack of) perseverance, (lack of) premeditation, sensation seeking, and positive urgency. Items were rated on a 4-point scale from Strongly Agree to Strongly Disagree.

Average scores were calculated for each item. Internal consistency was good across all UPPS-P dimensions in the present sample (α = .82-.93).

Alcohol Use

Alcohol use was calculated as average drinks per week over the most recent four-month period prior to study completion, and was compiled by combining LHC-reported frequency and quantity of alcohol use during the four-month period. Participants selected from five choices describing how *frequently*, on average, they used alcohol during each period (1 = once per month or less, 2 = once per week, 3 = two or three times per week, 4 = four or five times per week, 5 = every day). Participants selected from seven choices describing the *average amount* of alcohol they used per occasion during each period (1 = one drink, 2 = two drinks, 3 = three drinks, 4 = four drinks, 5 = five drinks, 6 = six to ten drinks, 7 = ten or more drinks). From these responses, an *average weekly alcohol use* variable was computed. First, responses for average amount of alcohol consumed were recoded so that each response represented a discrete number of drinks; for responses that originally represented a range, the midpoint was used, and ten drinks was used for the uppermost category. Next, responses for average alcohol use were recoded so that the resulting values represented an average number of drinking occasions per week. Finally, the product of the recoded variables was calculated to index the average number of drinks per week consumed by each participant in the most recent four-month period (average weekly alcohol use).

Data Analysis

Analyses were conducted using SPSS version 21.0. Multinomial logistic regression (MLR) allows for the simultaneous examination of effects of several independent variables (UPPS-P dimensions, alcohol use) on a categorical variable with more than two discrete outcomes (smoking status: non-smoker, non-daily smoker, or daily smoker). The model estimated the effects of the independent variables on the log odds (or logit) of belonging to 1) either non-daily or daily smoking categories compared to the non-smoking category as a reference, and 2) daily smoking category compared to the non-daily smoking category as a reference. Coefficients for each variable were exponentiated to provide an odds-like ratio for risk of a smoking category membership compared to the reference group; this value is not a true odds ratio due to the portion of the sample being excluded for either smoking outcome (Peng & Nichols, 2003).

Results

Table 2.1 summarizes correlations between UPPS-P, alcohol, and tobacco use categories. Consistent with previous literature, UPPS-P variables were significantly intercorrelated, with few exceptions. All UPPS-P dimensions were positively correlated with weekly alcohol use. UPPS-P dimensions and alcohol were correlated with tobacco use categories using data from: 1) non-smokers and non-daily smokers, 2) non-smokers and daily smokers, and 3) non-daily smokers and daily smokers, with smoking status dummy-coded. Relative to non-smokers, non-daily smoking was correlated with all dimensions of the UPPS-

P except sensation seeking, whereas daily smoking was significantly positively correlated with all dimensions of the UPPS-P. Both categories of smoking status were positively correlated with increased alcohol use relative to non-smokers. Relative to non-daily smokers, only negative and positive urgency were significantly positively correlated with status as a daily smoker.

Gender (male = 1), and age were also included as potential correlates of impulsivity and smoking group status. Gender was significantly positively correlated with sensation seeking, positive urgency and alcohol use (Table 2.1); however, gender was not significantly related to either smoking category and was thus not included in subsequent analyses. Age was not significantly different across groups, and was not correlated with any study variables; therefore, it also was not included in any subsequent analyses.

Impulsivity and alcohol use predicting smoking status

A MLR analysis was conducted examining the independent effects of UPPS-P and weekly alcohol use on the odds-like ratios of belonging to the two categories of smoking status, relative to being a non-smoker, and belonging to the daily smoking group, relative to non-daily smoking. Due to the high correlation between positive urgency and negative urgency and the similar correlations between these two dimensions and smoking categories, positive urgency was excluded from the analyses to reduce multicollinearity. The Likelihood Ratio test demonstrated significant improvement of the MLR model over the intercept-only or null model ($\chi^2 = 83.35$, $p < .001$). Statistical significance

of individual predictors was tested using the Wald chi-square statistic, with negative urgency (χ^2 = 17.97, p < .001) and alcohol use (χ^2 = 18.65, p < .001) emerging as the only significant individual predictors in the overall model. (Lack of) premeditation (χ^2 = 4.89, p = *.087.*) and (lack of) perseverance (χ^2 = .75, *p=.09*) demonstrated a trend toward significance. Sensation seeking (χ^2 = 2.02, *p=.37*) was not a significant predictors of group membership.

Odds-like ratios with corresponding 95% confidence intervals are presented in Table 2.2. Weekly alcohol use was a significant predictor of both non-daily and daily smoking status relative to nonsmoking status. (Lack of) premeditation significantly predicted membership in the non-daily smoking group relative to non-smokers, with a one standard deviation increase in (lack of) premeditation associated with a 44% increase in the likelihood of being a non-daily smoker relative to a non-smoker. Negative urgency significantly predicted membership in the daily smoking group relative to non-smokers, with a one standard deviation increase in negative urgency associated with an approximately two-fold increase in the likelihood of being a daily smoker relative to a non-smoker. An equivalent MLR model was estimated using non-daily smoking as a reference group in order to provide a comparison between non-daily and daily smokers. Negative urgency was also a significant predictor in this comparison, with a one standard deviation increase associated with a 77% increase in the likelihood of being a daily smoker, rather than a non-daily smoker.

Discussion

The purpose of Study 1 was to investigate the associations between impulsivity, alcohol use, and smoking frequency in young adult first-year college students who varied in frequency of cigarette smoking. UPPS-P dimensions of negative urgency, positive urgency, (lack of) premeditation, (lack of) perseverance, and alcohol use (drinks per week) were positively correlated with both non-daily and daily smoking, whereas sensation seeking was positively correlated only with daily smoking. Consistent with my hypotheses, alcohol use and negative urgency predicted increased risk of membership in the daily smoking group relative to the non-smoking group, and alcohol use predicted increased risk of membership in the non-daily smoking group. Contrary to my hypothesis, sensation seeking was not associated with status as a non-daily smoker. Finally, lack of premeditation was associated with status as a non-daily smoker, relative to non-smokers. These results demonstrated that alcohol consumption and lack of premeditation are associated with the onset of intermittent smoking, while alcohol and negative urgency are associated with the transition to daily smoking prior to the college experience.

As hypothesized, alcohol use was associated with status as a non-daily and daily smoker relative to non-smokers, which is consistent with previous research demonstrating that alcohol is associated with tobacco use (Dierker et al., 2006; Harrison et al., 2008; Jackson et al., 2005; Shiffman et al., 2012; Weitzman & Chen, 2005). However, alcohol use did not differentiate non-daily from daily smokers, suggesting that alcohol use was associated with tobacco use

in general, but that other risk factors may influence transitions from non-daily to daily tobacco use in individuals who become daily smokers prior to entry into college.

One possible risk factor for transitioning to heavier patterns of tobacco use is negative urgency. Previous studies have identified urgency as a risk factor for problematic tobacco use and dependence (e.g. Billieux et al., 2007; Doran et al., 2009; Spillane et al., 2010). In this study, negative urgency was correlated with both non-daily and daily smoking, but it was a unique risk factor only for daily smoking, providing additional evidence for the potential role of negative urgency in heavier tobacco use. Previous research has also found that negative urgency is predictive of other problematic behaviors in addition to frequent smoking (e.g. aggression, risky sex, problem drinking, illegal drug use; Settles et al., 2012), suggesting that behaving impulsively when upset may increase vulnerability to a variety of risk-related behaviors, including tobacco dependence.

Unexpectedly, sensation seeking was not associated with non-daily smoking, despite previous studies demonstrating that high sensation seekers experience increased reinforcement from tobacco use (Perkins, Gerlach, Broge, Grobe, & Wilson, 2000) and that adult non-daily smokers report smoking for the positive reinforcing effects of tobacco (Shiffman et al., 2012). This may be due to the age and smoking status of the population in this study. Previous research has identified non-daily smoking in young adults as a period of transition between heavier use, or quitting altogether (White et al., 2009), suggesting that the group of non-daily smokers in this study may in fact be composed of a heterogeneous

group of individuals who may be in a transitional stage of tobacco use. Interestingly, lack of premeditation was a unique risk factor for non-daily smoking in this study. It is possible that this group of non-daily smokers represents a subset of smokers that are more likely to smoke on occasion because they are less sensitive to the long-term consequences of smoking (i.e. tobacco dependence, negative health effects). However, these results should be interpreted with caution as the Wald-chi square estimate for lack of premeditation was only trending toward significance, suggesting that the association between lack of premeditation and non-daily tobacco use is modest at best.

There were several limitations to the current study that should be addressed. First, the study design was cross-sectional in nature, so I was not able to determine causal relationships between impulsivity, alcohol use, and cigarette smoking. Though these results suggest that alcohol is a risk factor for cigarette smoking in general, and negative urgency may increase risk for daily use and dependence, longitudinal and experimental research would be required to elucidate these possibilities. Second, concurrent alcohol and tobacco use was not assessed in this study. Impulsivity, and in particular lack of premeditation, has been linked to concurrent alcohol and tobacco use in a previous study of young adult current smokers (VanderVeen et al., 2013). Lack of premeditation and alcohol use were both correlated with both non-daily and daily smoking, and lack of premeditation emerged as a unique risk factor for non-daily smoking, so it is possible that those high in lack of premeditation may have used alcohol and tobacco concurrently in our study sample. However, more detailed data on

concurrent tobacco and alcohol use is needed to further evaluate the potential relationship between impulsivity and concurrent alcohol and tobacco use. In addition, dimensions of alcohol use aside from average drinks per week (e.g. quantity of drinks per drinking occasion, frequency of alcohol use, symptoms of alcohol abuse and dependence) were not assessed. Future studies should include multiple measures of alcohol use, which may further inform the relationship between alcohol use and smoking. Third, cigarette smoking frequency was assessed using self-reported assessments, which may be subject to recall bias. Future studies should incorporate objective measures to verify smoking status. Finally, the study population consisted of young adult college students, so the interpretation of these results may not be generalizable to other age groups.

Despite the limitations of the study, these results demonstrate that alcohol, lack of premeditation and negative urgency are risk factors for tobacco use in young adults. While this study provides some indication of the risk factors for non-daily and daily smoking status at a single time point, entrance into college, Study 2 will expand upon this line of research by assessing impulsivity and alcohol use to determine which dimensions are associated with increases in tobacco use across a three year period using longitudinal trajectory modeling.

Table 2.1: Correlations between UPPS-P, Alcohol and Smoking Status

	1	2	3	4	5	6	7
1. NU							
2. PRE	.39***						
3. PER	.32***	.38***					
4. SS	.09*	.36***	.03				
5. PU	.73***	.47***	.32***	.25***			
6. Alcohol	.21***	.29***	.10*	.25***	.25***		
7. Gender (Male vs Female)	.01	.08	.06	.30***	.16**	.10**	
ND vs. NS (n=460)	.15**	.20***	.10*	.09	.14**	.27***	.09
D vs. NS (n=441)	.28***	.24***	.15**	.14**	.25***	.24***	.01
D vs. ND (n=103)	.26**	.11	.11	.11	.24*	-.01	.11

$p < .05$, ** $p < .01$, *** $p < .001$

Note: NU = negative urgency, PRE = (lack of) premeditation, PER = (lack of) perseverance, SS = sensation seeking, PU = positive urgency, ALC = average weekly alcohol use (previous year), NS = non-smoker status, ND = non-daily smoker status, D = daily-smoker status. N = 500, except where noted.

Table 2.2: Odds-like ratios (with 95% confidence intervals) for UPPS-P factors (standardized values) and average weekly alcohol use on non-daily and daily smoking statuses relative to non-smoking

Category	Predictors	Exp(B)	95% CI	p-value
Non-Daily vs. Non-Smokers	NU	1.29	0.93 – 1.78	.13
	PRE	**1.44***	**0.93 – 2.04**	**.05**
	PER	1.08	0.78 – 1.50	.64
	SS	1.01	0.73 – 1.39	.98
	ALC	**1.09*****	**1.05 – 1.14**	**<.001**
Daily vs. Non-Smokers	**NU**	**2.28*****	**1.53 – 3.40**	**<.001**
	PRE	1.32	0.87 – 2.02	.19
	PER	1.17	0.80 – 1.70	.42
	SS	1.33	0.89 – 1.98	.17
	ALC	**1.07*****	**1.02 – 1.13**	**<.01**
Daily vs. Non-Daily Smokers	**NU**	**1.77***	**1.12 – 2.81**	**.02**
	PRE	0.92	0.57 – 1.51	.75
	PER	1.08	0.70 – 1.67	.73
	SS	1.32	0.83 – 2.11	.25
	ALC	0.98	0.93 – 1.04	.51

Note: NU = negative urgency, PRE = (lack of) premeditation, PER = (lack of) perseverance, SS = sensation seeking, PU = positive urgency, ALC = average weekly alcohol use (previous year), Non-daily = non-daily smoker status, Daily = daily smoker status

Chapter Three: Study 2 - Longitudinal Study Examining the Association between Impulsivity, Alcohol Use and Developmental Trajectories of Cigarette Smoking in Young Adults

Introduction

Results from Study 1 indicated that alcohol use and impulsivity were associated with increased risk for smoking prior to enrollment in college. Weekly alcohol use was associated with non-daily and daily smokers relative to non-smokers, but did not differ between smoking groups. UPPS impulsivity also differentiated smoking groups; compared to non-smokers, lack of premeditation was associated with non-daily smoking, and negative urgency was associated with daily use. Study 2 expands upon the results of Study 1 by examining the role of alcohol use and impulsivity in smoking across the first three years of college. The longitudinal approach will enable a more precise examination of these risk factors by identifying the factors that are most strongly associated with young adults who initiate smoking and escalate in frequency of use across the three-year period of the study.

Previous longitudinal studies examining tobacco use across adolescence and young-adulthood have demonstrated that trajectories of tobacco use are heterogeneous, and that initiation and escalation of smoking occur in both adolescent and young-adult age groups. In one of the initial studies to use longitudinal data to identify heterogeneous developmental trajectories of cigarette smoking, Chassin et al. (2000) identified 6 distinct trajectories of smoking behavior (two a-priori and four using empirical methodology) in a sample of 8,556

individuals. The two trajectories identified a priori were “non-smokers” and “erratic” smokers. A group-based trajectory approach (Nagin, 1999) was used to empirically identify four additional trajectories: early stable smokers (12% of the sample) who started smoking at a young age (12-13 years old) and then progressed to daily smoking by the age of 15; late stable smokers (16%) who reported smoking infrequently until the age of 18, then escalated to daily patterns of use by the age of 24; experimenters (6%) who had early onset of infrequent smoking, but did not escalate to daily use and quit by the age of 20; and quitters (5%) who started smoking late in adolescence and escalated to daily smoking patterns, followed by a decline until quitting altogether by the age of 25. Subsequent studies have generally found four trajectory groups that are comparable in shape to those found in Chassin et al. (2000): a consist of a non-smoking group, a late-escalating group, a decreasing group, and a heavy/stable smoking group (e.g. J. Brook et al., 2006; D. Brook et al., 2008; Caldeira et al., 2012). A fifth group, defined by relatively stable levels of occasional smoking, has also been identified (D. Brook et al., 2008; Caldeira et al., 2012). While the specific number and shape of the trajectories identified in each study varies slightly based upon sample size and the timeframe for assessments, these studies confirm the heterogeneity in trajectories of tobacco use and underscore the importance of young adult escalating smokers. Accounting for heterogeneity in the trajectories of tobacco use is important when identifying risk factors that may increase the vulnerability for tobacco use escalation, in order to better guide

development of prevention and intervention programs aimed at reducing tobacco use in young adult populations.

Much of the previous research examining longitudinal trajectories of tobacco use has focused on identification of risk factors predicting smoking uptake in adolescents; risk factors that predict escalation in young adults have not been examined in detail. Late-escalators (i.e., young adults) are similar to non-smokers on several risk factors during adolescence (i.e. few friends and relatives who smoke, high negative beliefs about smoking, low delinquency, high levels of parental support; J. Brook et al., 2006; Chassin et al., 2000), suggesting that risk factors predicting smoking escalation in adolescents are different from those predicting escalation in young adults. However, more research is needed to specifically address potential risk factors for smoking escalation in studies specifically examining young adults.

As identified in the introduction to this dissertation, multiple cross-sectional studies have shown that concurrent alcohol use increases smoking in both non-daily and daily smokers (Harrison & McKee, 2008; Krukowski, Solomon, & Naud, 2005; Shiffman & Paty, 2006). Event-level analyses have also found that both non-daily and daily smokers consistently increase smoking in situations where alcohol is consumed (Jackson, Colby, & Sher, 2010; Witkiewitz et al., 2012). In addition, increasing evidence has identified alcohol use as a risk factor for long-term escalation of tobacco use. For example, cross-sectional and longitudinal studies have found that past-year alcohol consumption increases the likelihood of smoking initiation, and binge alcohol use is associated with increases from non-

smoking to heavier patterns of use (Reed et al., 2007; 2010; White et al., 2009). Furthermore, Caldeira et al. (2012) examined developmental trajectories of smoking behavior in young adult college students and found that greater alcohol use and symptoms of alcohol dependence in the first year of college were risk factors for the development of daily smoking relative to non-smokers, particularly for males. Taken together, these studies suggest that alcohol use is a risk factor for both situational and long-term increases in tobacco use, and should be taken into consideration when identifying risk factors for smoking escalation in young adults.

Longitudinal designs are proficient at identifying distinct trajectories of tobacco use and risk factors associated with smoking escalation, but few longitudinal studies have directly addressed the role of trait impulsivity as a predictor of trajectory group membership. Of the studies that have examined impulsivity as a potential predictor, both sensation seeking and disinhibition have been associated with membership in heavier smoking groups relative to more occasional and/or non-smoking groups (D. Brook et al., 2008; White, Pandina, & Chen, 2002). However, these studies used a unidimensional measurement of impulsivity, thus limiting the ability to determine the unique role of the multi-dimensional construct on smoking group membership. Cross-sectional research, including the results from Study 1, have examined the relationship between impulsivity and tobacco use using multidimensional assessments and have identified distinct dimensions of impulsivity (i.e. sensation seeking, lack of premeditation, and urgency) that are associated with smoking initiation and

dependence (i.e. Billieux et al., 2007; Doran et al., 2009; Perkins et al., 2000, 2008; Spillane et al., 2010). This underscores the need for more longitudinal research examining impulsivity and tobacco use using multidimensional assessments.

Similar to measures of trait impulsivity, few longitudinal studies have addressed the role of behavioral impulsivity on the developmental trajectories of smoking behavior. Cross-sectional studies indicate that current smokers discount rewards at a greater magnitude than non-smokers (Bickel et al., 1999; Heyman & Gibb, 2006; Mitchell, 1999; Reynolds & Fields, 2012), make more risky decisions on the Balloon Analog Risk Task (Lejuez et al., 2003), and have greater numbers of inhibitory errors on a stop signal task (Billieux et al., 2010), but there is still some uncertainty whether differences in behavioral impulsivity are a cause of, or a determinant of current smoking status. Audrain-McGovern et al. (2009) examined delay discounting in a longitudinal study spanning from mid-adolescence to young adulthood and found that baseline delay discounting was higher in smoking groups relative to non-smokers. However, delay discounting remained relatively stable in both smoking and non-smoking groups across the study, suggesting that behavioral impulsivity did not change as a function of long-term exposure to tobacco and providing evidence for the stability of behavioral impulsivity over time, but more research is needed to identify dimensions of behavioral impulsivity as risk factors for smoking, and verify the stability of the tasks in individuals who escalate in cigarette smoking.

Taken together, the accumulated evidence suggests that developmental trajectories of smoking behavior are heterogeneous, and that a subset of young adults escalate to regular tobacco use. However, more research is needed in order to identify risk factors associated with smoking escalation in this age group. Data from a three-year longitudinal study of tobacco use among college students at the University of Kentucky was analyzed in order to: 1) identify developmental trajectories of smoking in young adults across a three-year period of college using group-based trajectory modeling, 2) examine dimensions of impulsivity and characteristics of alcohol use as potential risk factors that increase the likelihood of belonging to a smoking trajectory relative to a non-smoking trajectory, and 3) determine if alcohol use and/or behavioral impulsivity increases over the course of the study in escalating smokers. Each dimension of impulsivity was assessed during freshman year and included as a risk factor that could potentially increase the likelihood of belonging to a smoking trajectory that escalated in use over the subsequent two years of the study.

Group-Based Trajectory Modeling

Group-based trajectory modeling was the statistical method applied to identify developmental trajectories and potential risk factors for smoking group membership in this study. Group-based trajectory modeling is a statistical tool for measuring and explaining differences in the developmental course of a particular behavior across a population, which is otherwise known as a developmental trajectory (Nagin, 1999; Nagin & Tremblay, 2005). Group-based

trajectory modeling has advantages over other longitudinal statistical methods (e.g. multivariate analysis of variance, structural equation modeling) when a particular behavior being analyzed is thought to follow a multinomial pattern where the strengths and the directions of change vary between individuals (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009). As described in Andruff et al. (2009), standard growth models assume that individuals in a given sample are expected to change in the same direction across time. While the degree of change may vary between individuals, the overall growth curve is modeled using a single trajectory. In these models, researchers can use categorical or continuous variables as predictors to explain potential individual differences in the slope or intercept of the growth curve. However, a standard growth curve would not be optimal for the current study, since previous research has demonstrated that trajectories of tobacco use are heterogeneous, with individuals displaying increasing, decreasing, and stable patterns of tobacco use across time.

In comparison, group-based trajectory modeling does not assume that individual differences occur apart from a single growth curve function, but may be a set of distinguishable classes in and of themselves (Nagin & Tremblay, 2005). Although a particular behavior in a given population is continuous distributed, using groups to approximate developmental trajectories allows for modeling an unknown distributional shape where individuals in the population are not following a common developmental process of growth or decline. It is important to note that the resulting groups are approximations, and not literal entities.

Group-based trajectory modeling assumes that individual differences in trajectories can be summarized by a finite set of different polynomial equations across age or time, with each equation corresponding to a different trajectory (Nagin & Tremblay, 2005). The most parsimonious group structure for a given dataset is obtained by modeling the predicted trajectory of each group, along with the posterior probabilities that a randomly chosen individual from the sampled population is a member of each such trajectory group. These steps are generally accompanied by an a priori hypothesis predicting the maximum possible distinct trajectories that best fit the distribution of individual trajectories.

Study Hypotheses

In the current study, it was hypothesized that: 1) there would be four smoking groups defined by distinct patterns of tobacco use that emerged over the 3 year time period, stable non-smokers, declining smokers (those who smoked prior to study entry and then quit over the course of the 3 year period), escalating smokers (those who increased cigarette use over time), and stable daily smokers; 2) frequent alcohol use would be associated with escalation of cigarette smoking; and 3) self-report trait measures of impulsivity would increase the probability of belonging to the escalating smoking trajectory, with higher scores on sensation seeking and urgency associated with escalation and heavy use, respectively.

Method

Participants and Procedures

Screening and enrollment procedures were identical to Study 1. Participants in the longitudinal study were composed of 525 college students (48.1% male: mean age at first assessment = 18.95 years, sd = 0.77).

The study consisted of assessments, which occurred annually for three consecutive years. Assessments consisted of answering questions about substance use and personality, and completing computer-based laboratory tasks. Each assessment took approximately 2.5 hours to complete.

Drug Use

At each assessment, participants completed a life history calendar of their substance use (LHC; Caspi et al., 1996). During the initial assessment, participants are asked to report on their substance use beginning when they were 13 years old up until the time of the assessment. Each year was divided into three four-month segments that correspond roughly to the two parts of the school year and the summer. Follow-up assessments were completed one and two-years following the initial assessment. For these assessments, participants were asked to report on their drug use across the last twelve months in one-month increments. Thus, the multiple administrations of the LHC assessed independent periods of time.

Tobacco use was assessed by asking participants to rate smoking frequency using a 0-5 scale: 0 = no smoking, 1 = once per month or less, 2 =

once per week, 3 = two or three times per week, 4 = four or five times per week, and 5 = every day. To ensure convergence of trajectory model fitting algorithms, smoking frequency was aggregated across the assessments by including only the three most recent 4-month data points prior to the first assessment (i.e., smoking in the year prior to study entry). A total of 11 data points were examined for each individual (3 intervals prior to assessment 1, and 4 intervals prior to assessments 2 and 3).

Risk Factors

Personality and Behavioral Assessments

The trait impulsivity assessment consisted of the *UPPS-P* (Whiteside & Lynam, 2001). Details for this measure are summarized in Study 1. UPPS positive urgency was not included in the analyses for Study 2 in order to reduce multicollinearity due to the high correlation with negative urgency (r = 0.73).

The Monetary Choice Questionnaire (MCQ; Kirby, Petry, & Bickel, 1999) - This behavioral inhibition task consists of 27 questions assessing equivalence value of immediate versus delayed monetary rewards. For each item, individuals are asked whether they would prefer a certain monetary amount today, or a different amount at a later time. Delay times and monetary values differ for each item, with delay times ranging from 7 to 160 days, and monetary amounts ranging from $11 to $85. Each of the 27 choices on the MCQ are used to assign an overall approximation of discounting rates (i.e., k values) for each participant; larger k values signify greater temporal discounting and more impulsive choices.

Cued Go/No-Go Task (Marczinski & Fillmore, 2003) - This behavioral inhibition task consists of 250 trials examining reaction times (RT) to choice reaction time cues following stimuli having differential probabilistic relationships to RT cues. Each trial begins with the presentation of a black fixation point (+) on a white screen for 800 ms, followed by a 500 ms blank screen. A black rectangle stimulus is then presented on a white screen in horizontal or vertical orientation for varying intervals (100, 200, 300, 400, 500 ms). Standard Go and No Go cues are then presented as solid colors (blue or green) within the rectangles. Subjects are required to respond (i.e., key press) as quickly as possible whenever a green hue is presented and to not respond if the blue hue is displayed. Each hue is presented on 50% of trials (i.e., 125 of 250 trials) in a randomized order. The orientation of the rectangles (i.e., horizontal or vertical) have differential relationships with RT cues. Vertical boxes precede Go cues (i.e., green hue presentation) on 80% of trials (i.e., 100 trials) and No Go cues (i.e., blue hue presentation) on 20% of trials (i.e., 25 trials). In contrast, the horizontal box display precedes No Go targets on 80% of trials and 'Go' targets on 20% of trials. The task requires 15 minutes to complete. Dependent measures include response inhibition (i.e. proportion of no-go targets in which a participant fails to inhibit a response) and response activation (i.e. reaction time to the go targets).

Balloon Analog Risk Task (BART; Lejuez et al., 2002) – This behavioral inhibition task examines risky decision-making. Simulated balloons are inflated on a computer by clicking a mouse button. A successful inflation results in an addition of money to a temporary bank and increases the probability of the

balloon popping on the next inflation. If a subject chooses to stop inflating a balloon and move to another balloon, the amount of money accrued in the temporary bank is placed in a permanent bank; if a subject chooses to inflate the balloon and it pops, money in the temporary bank is lost. Dependent measures are the number of popped balloons, and the number of clicks per unpopped balloon.

Alcohol Use

Alcohol use was calculated as average drinks per week (see Study 1 for details on calculations). Reports of use were aggregated across the 4-month intervals prior to each of the three yearly assessments to create three consecutive one-year averages.

Data Analysis

Group-based trajectory modeling (Jones, Nagin, & Roeder, 2001; Nagin, 1999; 2009) with a zero-inflated Poisson (ZIP) distribution was used to empirically cluster individual participants' smoking trajectories to identify a satisfactory parsimonious group structure, using SAS proc traj (Version 9.3). A zero-inflated Poisson distribution (ZIP) was used to model the smoking frequency data in order to account for excess zeroes that were present as a function of non-smokers in the current sample. The Bayesian Information Criteria (BIC; Jones et al., 2001; Nagin, 2009) was applied to determine the optimal number and shape of the trajectories by examining the alteration in BIC with each change in number and shape of distinctive group trajectories. A smaller BIC indicated an

improvement in model fit. Jones et al. (2001) outlined procedures for model selection based upon interpretation of the change in the BIC, using an approximation of the log Bayes factor. The approximation is calculated by 2*ΔBIC [where ΔBIC is the change in BIC between a more complex model versus the simpler (or null) model]. Using this calculation, a difference (i.e., change in the BIC) that is between 0 and 2 represents weak evidence for the more complex model over the null model, a change between 2 and 6 represents moderate evidence, a change between 6 and 10 represents strong evidence, and anything greater than 10 represents very strong evidence. Next, posterior probabilities were calculated for each individual to estimate the probability of belonging to each trajectory group, and group size was determined by calculating the percentage of individuals with the highest probabilities for belonging to each group. Average posterior probabilities can be used to evaluate the internal reliability for each trajectory, and were included in the assessment of the overall model fit. According to Nagin (2009), average posterior probabilities above a 0.7 threshold indicate that the modeled trajectories accurately grouped individuals with similar patterns of behavior.

After determining the number and shape of the smoking trajectories, individual differences in dimensions of trait (UPPS-P) and behavioral impulsivity (cued go/no-go, MCQ, BART), and average weekly alcohol use assessed in year 1 were included in the model as risk factors that could influence the probability of group membership. A p-value was assigned for whether each risk factor changed the likelihood of being in a smoking trajectory relative to being in the

non-smoker trajectory, which was designated as a reference category. Parameter estimates and resulting p-values for alcohol use, and trait and behavioral impulsivity were evaluated separately to determine significance of each dimension of impulsivity on smoking group membership. The resulting dimensions of trait and behavioral impulsivity that were significant predictors of smoking group membership were included in a final model along with alcohol use to determine which factors had the greatest impact on probability of group membership. Coefficients for each risk factor were exponentiated to provide an odds-like ratio for risk of a smoking trajectory group membership compared to the non-smoking trajectory.

Finally, linear mixed models were used to examine changes in behavioral inhibition and alcohol use over the three-year period in each trajectory group. Because the average posterior probabilities of group membership were high across trajectory groups (range of average posterior probabilities .96 - .99, see Table 3.3) individuals were assigned to the group to which their probability of belonging was the highest, and group assignment was included as a categorical independent predictor (4 levels) along with wave (3 levels). Dependent measures were behavioral impulsivity (i.e. cued go/no-go proportion of inhibitory errors, MCQ overall k, and BART responses per unpopped balloon), and average weekly alcohol use.

All analyses were conducted using proc traj and proc mixed in SAS, version 9.3. Data analysis was restricted to individuals with at least seven data points (i.e. a minimum of two waves of data). Proc traj can account for data

missing completely at random, however participants with less than seven data points were considered to have missing data due to attrition and were excluded from the model in order to mitigate bias in model fitting. A total of 96 participants with less than seven data points were excluded from the analysis, resulting in a sample size of 429. Hypothesis test results were considered significant at $p<.05$.

Results

Selection of Trajectory Model

Table 3.1 presents the BIC for each group model evaluated, and the resulting change in BIC obtained with each additional group added to the model. First, a single group model was specified, and additional groups were added in one at a time until the maximum number of 5 groups was reached. Although I hypothesized that a four-group model would provide the best overall fit, a five group model was tested to account for the potential low-stable smoking group found in Caldeira et al. (2012). The four-group model had the smallest BIC compared to the models with one-, two-, and three-groups. A five-group model was tested but did not converge. After determining the optimal number of groups, parameter estimates for linear and quadratic polynomial functions were evaluated to determine the optimal shape for the trajectory of each group, starting with all quadratic functions for the smoking trajectories. Group-based trajectory modeling allows for modeling of polynomial functions up to the cubic order but models starting with all quadratic polynomial functions provided a better fit (i.e. a lower BIC).

Table 3.2 displays the fitted group membership probabilities as well as the estimates and standard errors for the parameters of the selected four-group model. Eliminating a non-significant quadratic function from the fourth group resulted in a moderate improvement to the model, with a change in BIC from -2353.45 to -2350.52; $2*\Delta BIC = 5.86$). However, the inclusion of risk factors resulted in a convergence failure so the four-group model with quadratic functions for each group was retained as the final model. Table 3.3 displays the average posterior probabilities of group membership for the final four-group model. Average posterior probabilities were high (above .95 for all groups), which verified the internal reliability of the final four-group model.

The resulting trajectories for the four-group model are displayed in Figure 3.1. Non-smokers (72.6% of the sample, 45% male) were characterized by smoking frequencies that were near zero throughout the duration of assessment. High stable smokers (13.1% of sample, 55% male) were composed of daily smokers as well as frequent non-daily users (average 2 – 3 times per week) who modestly increased use to 4 – 5 times per week by the end of the study. Decreasing smokers (8.7% of sample, 45% male) were characterized by frequent smoking prior to college entry, followed by decreasing patterns of use during college. Late-escalating smokers (5.6% of sample, 83% male) initiated smoking following college enrollment, then escalated in smoking frequency across the first two years of college. All trajectory groups were similar in age at first assessment (M = 18.9 years old, SD = 0.1).

Risk Factors Associated with Developmental Trajectories of Smoking Frequency

Group means and standard deviations of predictor variables of interest are presented in Table 3.4. Three separate models were used to identify risk factors that differentiated participants' trajectory group membership; the first model tested initial assessments of alcohol use, model two tested initial assessments of UPPS impulsivity dimensions, and the third model tested initial assessments of behavioral impulsivity. Since males accounted for 83% of the late-escalating smoking group, gender was also included as a potential risk factor in each of the analyses. Parameter estimates, standard errors, and *p*-values for the analyses are presented in Tables 3.5, 3.6 and 3.7. Across all three models, gender (male) increased the probability of belonging to the late-escalating smoking group. Relative to non-smokers, alcohol use significantly increased the probability of belonging to the high stable and decreasing smoking groups (Table 3.5). UPPS-P sensation seeking significantly increased the probability of belonging to both the late-escalating and high-stable smoking groups, and negative urgency and lack of premeditation increased the probability of belonging to the high stable group (Table 3.6). No measure of behavioral impulsivity significantly altered group membership probabilities (Table 3.7).

Significant predictor variables from the separate analyses (i.e. gender, alcohol use, sensation seeking, negative urgency, and lack of premeditation) were entered simultaneously into a final model in order to determine the adjusted influence of the significant risk factors on probabilities of group membership. Table 3.8 summarizes estimates of odds-like ratios and 95% confidence intervals

for the significant predictor variables to determine the ratio of the probability of group membership in each smoking group compared to the probability of reference group membership (hereafter abbreviated as “likelihood” of group membership for ease of exposition). Each smoking trajectory was compared to the non-smoking group as a reference, and the high-stable group was compared to the late-escalating smoker group to determine risk factors associated with membership in each group. Alcohol use significantly predicted membership in the decreasing and high stable smoking groups relative to non-smokers. A one-standard deviation increase in drinks per week was associated with an estimated 67% increase in the likelihood of being in the decreasing smoking group, and an estimated 70% increase in the high stable smoking group. Sensation seeking and gender significantly predicted membership in the late-escalating smoking group relative to non-smokers. A one-standard deviation increase in sensation seeking was associated with an estimated 2-fold increase in the likelihood of being in the late-escalating smoking group, while male gender status was associated with an estimated 4-fold increase. Negative urgency significantly predicted membership in the high stable smoking group relative to non-smokers, with a one-standard deviation increase in negative urgency associated with an approximately 2-fold increase in the likelihood of being in the high stable smoking group. When the late-escalating smoking group was compared to high stable smokers, a one-standard deviation increase in negative urgency and alcohol use were associated with an approximately 3-fold and 99% increase in the likelihood of being a high stable smoker, respectively.

Variation in Alcohol Use and Behavioral Inhibition as a Function of Yearly Assessment and Trajectory Group Membership

Figures 3.2 – 3.5 display the variations in behavioral inhibition and alcohol use as a function of trajectory group membership and wave. Gender was included as a covariate for all analyses. Figure 3.2 displays average alcohol use, which varied as a function of an interaction between group membership and wave [$F(6,729) = 3.93$, $p<.001$]. Simple effects indicated that alcohol use increased across the three assessments in the late-escalator smoking group. In addition, high stable and decreasing smoking groups reported using alcohol more frequently across all three assessments relative to non-smokers. A main effect of group on cued go/no-go inhibition errors (Figure 3.3) [$F(3,418) = 2.83$, $p<.05$] with follow-up testing indicating that inhibition errors were higher in late-escalating smokers relative to the other trajectory groups. A main effect of assessment was found on cued go/no-go proportion of inhibitory errors [$F(2,738) = 5.14$, $p<.001$], and BART responses per unpopped balloon (Figure 3.4) [$F(2,718) = 4.80$, $p<.01$]. Follow-up tests revealed that proportion of inhibition errors increased and responses per unpopped balloon decreased over time. There were no significant differences as a function of smoking group or time on MCQ overall K (Figure 3.5).

Discussion

The purpose of this study was to: 1) identify distinct trajectories of smoking behavior in young adults across a three-year period, 2) examine alcohol use and dimensions of impulsivity as potential risk factors that increased the likelihood of belonging to a smoking trajectory group relative to non-smokers, and 3) determine if alcohol use and/or behavioral impulsivity increased across the smoking groups during the duration of the study. Four distinct trajectories of smoking frequency were identified: non-smokers (72.2%), decreasing smokers (9.2%), late-escalating smokers (5.3%), and high stable smokers (13.3%). Males were more likely to belong to the late-escalating smoking group, but no other gender differences were found. Initial alcohol use (assessed in year 1) increased the likelihood of belonging to groups that reported heavier smoking during initial assessments (i.e. high stable and decreasing smoking groups), and alcohol use also increased across the three yearly assessments in the late-escalating smoker group. Impulsivity was also associated with the likelihood of belonging to a smoking group. Sensation seeking increased the likelihood of being classified as a late-escalating smoker, whereas negative urgency increased the likelihood of being classified as a high-stable smoker. Behavioral impulsivity assessments in year 1 did not predict classification in any of the smoking groups, however cued go/no-go proportion of inhibition errors increased over the course of the study and errors were higher in the late-escalating smoker group, relative to non-smokers.

The trajectories that were identified in this study are comparable to the number and shape of trajectories found in other studies examining smoking in adolescents and young adults (e.g. Chassin et al., 2000; D. Brook et al., 2008; J. Brook et al., 2006). Moreover, the resulting trajectory groups identified in this study are generally consistent with those found in the Caldeira et al. (2012) study, which also examined trajectories of tobacco use in young adult college students across a four year period. The major difference between studies was that the current study did not identify a low-stable smoking group, which might be due to the relatively small sample size and more limited timeframe in the current study.

It is important to note that overall smoking rates were low across groups throughout the duration of the study. For example, the high stable group was composed of both non-daily and daily smokers, while the late-escalator group reported increasing tobacco use to approximately one occasion per week by the third year of the study. The lower rates of smoking found in this study are consistent with recent studies indicating that non-daily smoking is increasing in prevalence in both adolescent and adult smokers relative to daily smokers, further suggesting that the smoking rates observed in this study are indicative of a larger trend toward decreasing smoking rates (Schane et al., 2009; Shiffman, 2009b). This may be due in part to the rapidly evolving smoking bans and overall increases in the financial costs related to smoking (i.e. higher taxes on cigarette purchases; Ross, Blecher, Yan, & Hyland, 2011). Caldeira et al., 2012) also found that overall smoking rates were low across all groups of college students

during the four-year duration of that study. For example, the high stable smoking group was composed of both daily and non-daily (4-5 days per week) smokers, while the low-increasing smoking group escalated in use through the course of the study, but smoking levels remained fairly low and rose to approximately 15 days out of the month at the end of the fourth year of college. Importantly, even though the overall rates of smoking were low in Caldeira et al. (2012), those who were classified as high stable and low stable smokers still reported poorer health outcomes across the four-year duration of the study, suggesting that prevention and treatment interventions aimed at low-rate smokers are still warranted.

Consistent with my hypothesis, alcohol use was associated with more frequent tobacco use across the duration of the study, which supports the wide-body of research that has found a relationship between alcohol and tobacco use (e.g. Dierker et al., 2006; Harrison & McKee, 2008; Jackson et al., 2005, 2010; Krukowski et al., 2005; Reed et al., 2007, 2010; Shiffman & Paty, 2006; Weitzman & Chen, 2005; White et al., 2009; Witkiewitz et al., 2012). Initial (prior to college) alcohol use increased the likelihood of being classified in the high stable and decreasing smoking groups, both of which had heavier smoking patterns during first year assessments. Furthermore, alcohol use remained relatively stable in these groups across the three years of the study. Conversely, initial alcohol use did not increase the likelihood of belonging to the late-escalating smoking group, but alcohol use did increase across the three yearly assessments in this group, which supports previous research indicating that

alcohol and smoking are associated and increase at comparable rates (e.g. Orlando, Tucker, Ellickson, & Klein, 2005).

To my knowledge, this is the first study that has used the UPPS-P to examine dimensions of impulsivity as risk factors for smoking escalation in young adults. Previous studies using other sensation-seeking assessments have found that sensation seeking is associated with initiation (e.g. Lipkus et al., 1994), current smoking levels (Flory & Manuck, 2009; Spillane et al., 2010) and higher reports of the positive reinforcing effects of nicotine and tobacco (Doran et al., 2009; Perkins et al., 2000; 2008), which is consistent with the current findings and suggests that high sensation seekers are vulnerable to escalation of tobacco use as young adults.

Negative urgency increased the likelihood of being classified in the high stable smoking group relative to both non-smokers and late-escalators. While no longitudinal studies have examined urgency as a predictor of smoking, this finding is consistent with the results of Study 1 and with previous cross-sectional research indicating that urgency is associated with heavier tobacco use and dependence (e.g. Billieux et al., 2007; Doran et al., 2009; Spillane et al., 2010). However, because the high stable group reported smoking prior to study entry, more longitudinal research is needed to determine if negative urgency is a predictor of heavier use patterns in individuals prior to initiating smoking.

Measures of behavioral impulsivity did not predict group membership in this study. This is inconsistent with previous research indicating that delay discounting is associated with smoking status (e.g. Bickel et al., 1999) and

predicts smoking initiation in adolescents (Audrain-McGovern et al., 2009; Reynolds & Fields, 2012). However, delay-discounting levels did remain stable over the course of the study, indicating that escalation in smoking did not increase impulsive choice, which is consistent with previous research (Audrain-McGovern et al., 2009). Inhibitory errors on the cued-go no/go task increased across time, and the late-escalating smoking group had more inhibitory errors compared to the other groups. However, initial errors on the task in year 1 did not increase the likelihood of belonging to the late-escalator group. While this suggests that inhibitory control may decrease as a function of escalating tobacco use, the late-escalating smoking group represented a small proportion of the sample, so more research with larger sample sizes of escalating smokers is needed to confirm this finding. Finally, BART inflations per unpopped balloon decreased across the three-year duration of the study. However, this was unrelated to smoking group status and may reflect an overall decrease in risky decision-making as a function of age in the study sample.

There were several limitations to the current study that should be addressed. First, non-smokers in this study accounted for over 72% of the sample size, which resulted in a small number of participants in the three smoking groups. The late-escalating smoker group was particularly small (n = 23). Because of the small sample size, there might have been some power issues with the ability to detect predictor variables in the smoking groups. Therefore, these results should be replicated in subsequent longitudinal studies with larger sample sizes. Second, the late-escalating smoker group was

comprised almost exclusively of males. While a previous study found that males were more likely to be classified into a late-escalator smoking group (Caldeira et al., 2012) the proportion of males in that group represented 57%, which was significantly lower than the proportion of males found in the current study (83%). Though this suggests that males may be more vulnerable to late-escalation of tobacco use than females, this also limits the generalizability of sensation seeking and alcohol use as risk factors for late smoking escalation to males. Given the small sample size of the late-escalating smoking group, it is possible that the current result is subject to sampling error. Future studies with larger sample sizes are needed to address the gender differences observed in this study. Third, concurrent alcohol and tobacco use were not assessed in this study. Though the current assessments measured the frequency of cigarette and alcohol (drinks per week) use, more detailed data is needed to further evaluate the potential relationship between concurrent tobacco and alcohol use, and the role of other dimensions of alcohol use (e.g. binge drinking, symptoms of alcohol abuse/dependence) on long-term escalation of cigarette smoking. Finally, it should be noted that the current study used a limited number of behavioral impulsivity tasks. It is possible that other behavioral impulsivity tasks could engender performance that is more closely associated with tobacco escalation. Further research is needed examining behavioral impulsivity using a broader range of tasks in order to extend the results of the current study.

Despite the limitations of the current study, these results demonstrated that trajectories of tobacco use are heterogeneous in young adults, and risk for

escalation is not limited to adolescence. Furthermore, the results of the current study identified sensation seeking and urgency as risk factors for escalation and heavier patterns of tobacco use, and provided further confirmation that alcohol use is associated with heavier patterns of tobacco use. Given the health risks of engaging in tobacco smoking and the poor cessation rates among young adults who use tobacco both intermittently and daily, it is important to provide effective prevention and early intervention efforts aimed at curbing problematic tobacco use. Focusing on risk factors such as alcohol use, sensation seeking and negative urgency may increase the effectiveness of such prevention efforts that are associated with tobacco use.

Table 3.1: BIC values for group-trajectory models and log Bayes factor approximation to assess model fit

# Groups	BIC	Null Model	2*ΔBIC
1	-3481.66		
2	-2562.97	1	1897.94
3	-2403.46	2	274.18
4	-2353.45	3	100.10
5	Did not converge	4	n/a

Table 3.2: Parameter estimates and associated p-values for each trajectory group in the final four-group model

Trajectory Group	% of Sample	Parameter	Estimate (SE)	P-Value
Non-smokers	72.6%	Intercept	1.11 (0.19)	<0.001
		Linear	0.23 (0.10)	0.82
		Quadratic	-0.34 (0.01)	<0.001
Decreasing Smokers	8.7%	Intercept	-3.76 (0.90)	<0.001
		Linear	0.70 (0.66)	0.29
		Quadratic	-0.20 (0.11)	0.09
Late-Escalating Smokers	5.6%	Intercept	-3.39 (0.71)	<0.001
		Linear	0.71 (0.20)	<0.001
		Quadratic	-0.03 (0.02)	0.03
High Stable Smokers	13.1%	Intercept	1.34 (0.09)	<0.001
		Linear	0.02 (0.03)	0.46
		Quadratic	-0.001 (0.001)	0.65
ZIP Polynomial		Alpha 0	-0.03 (0.34)	0.93
		Alpha 1	-0.62 (0.19)	<0.001
		Alpha 2	0.03 (0.02)	0.05

Note: Parameters for each trajectory group included potential intercept, linear and quadratic trends. A linear trend tests for change in behavior across time occurring in a straight line (e.g. steadily increasing or decreasing). A quadratic trend tests for change in behavior across time that may increase, decrease or remain stable for a portion of the measurement, then change in either magnitude or direction. The ZIP polynomial function tests for changes in zero-counts in linear (Alpha 1) and quadratic (Alpha 2) trends.

Table 3.3: Average posterior probabilities of smoking trajectory group membership

	Average posterior probabilities				
Group Assignment	1	2	3	4	Range
1 Non-Smokers	**.964**	.010	.021	.005	.68 – 1.00
2 Decreasing Smokers	.003	**.995**	.003	.001	.50 – 1.00
3 Late-Escalating Smokers	.019	.000	**.970**	.010	.82 – 1.00
4 High Stable Smokers	.006	.000	.000	**.993**	.80 – 1.00

Table 3.4: Group means (SD) for alcohol use, UPPS and behavioral impulsivity measures assessed during the first year of the study

		Smoking Trajectory Group		
Risk Factor	Non-Smokers	Decreasing Smokers	Late-Escalating Smokers	High Stable Smokers
Alcohol Use	4.11 (5.87)	7.98 (6.43)	4.38 (4.48)	9.97 (9.07)
UPPS				
NU	2.15 (0.53)	2.30 (0.56)	2.27 (0.46)	2.60 (0.51)
PRE	1.93 (0.42)	2.07 (0.50)	2.00 (0.46)	2.30 (0.45)
PER	1.92 (0.41)	1.92 (0.41)	1.80 (0.45)	2.00 (0.43)
SS	2.94 (0.54)	3.06 (0.49)	3.25 (0.49)	3.20 (0.51)
Behavioral Impulsivity				
CGNG	0.05 (0.07)	0.05 (0.05)	0.09 (0.16)	0.04 (0.07)
BART	40.02 (11.57)	37.71 (10.08)	45.18 (12.66)	42.00 (9.36)
MCQ	0.03 (0.04)	0.04 (0.04)	0.04 (0.04)	0.02 (0.03)

Note: Alcohol use (average drinks per week), NU = negative urgency, PRE = (lack of) premeditation, PER = (lack of) perseverance, SS = sensation seeking, PU = positive urgency, CGNG = cued go/no-go proportion of inhibition errors, BART = Balloon Analog Risk Task, average inflations (per unpopped balloon), MCQ = Monetary Choice Questionnaire overall K.

Table 3.5: Parameter estimates and associated p-values for the effect of alcohol use and gender on the probabilities of trajectory group membership

Group Membership	Estimate (SE)	P-Value
Decreasing Smokers		
Alcohol (Drinks per Week)	**0.06 (0.16)**	**<0.001**
Gender	-0.12 (0.38)	0.76
Late-Escalating Smokers		
Alcohol (Drinks per Week)	-0.05 (0.30)	0.85
Gender	**1.61 (0.58)**	**<0.01**
High Stable Smokers		
Alcohol (Drinks per Week)	**0.73 (0.14)**	**<0.001**
Gender	0.17 (0.32)	0.59

Note: Gender = Male vs Female. Estimates are of log odds-like ratios of the probability of smoking group membership, relative to non-smokers.

Table 3.6: Parameter estimates and associated p-values for the effect of UPPS dimensions and gender risk factors on the probabilities of trajectory group membership

Group Membership	Estimate (SE)	P-Value
Decreasing Smokers		
Negative Urgency	0.23 (0.20)	0.26
Lack of Perseverance	0.13 (0.20)	0.49
Lack of Premeditation	0.20 (0.22)	0.38
Sensation Seeking	0.06 (0.21)	0.77
Gender	0.14 (0.38)	0.71
Late-Escalating Smokers		
Negative Urgency	0.29 (0.28)	0.31
Lack of Perseverance	-0.35 (0.27)	0.20
Lack of Premeditation	-0.11 (0.32)	0.72
Sensation Seeking	**0.70 (0.33)**	**0.03**
Gender	**1.57 (0.67)**	**0.02**
High Stable Smokers		
Negative Urgency	**0.82 (0.18)**	**<0.001**
Lack of Perseverance	0.00 (0.17)	0.98
Lack of Premeditation	**0.40 (0.19)**	**0.04**
Sensation Seeking	**0.39 (0.19)**	**0.05**
Gender	0.31 (0.34)	0.36

Note: Gender = Male vs Female. Estimates are of log odds-like ratios of the probability of smoking group membership, relative to non-smokers.

Table 3.7: Parameter estimates and associated p-values for the effect of behavioral inhibition and gender risk factors on the probabilities of trajectory group membership

Group Membership	Estimate (SE)	P-Value
<u>Decreasing Smokers</u>		
MCQ Overall K	0.18 (0.16)	0.25
CGNG P inhibitory errors	0.01 (0.20)	0.98
BART Responses per Balloon	-0.20 (0.19)	0.30
Gender	0.07 (0.38)	0.86
<u>Late-Escalating Smokers</u>		
MCQ Overall K	0.22 (0.21)	0.29
CGNG P inhibitory errors	0.27 (0.16)	0.09
BART Responses per Balloon	0.35 (0.23)	0.14
Gender	**1.62 (0.58)**	**<0.01**
<u>High Stable Smokers</u>		
MCQ Overall K	0.06 (0.15)	0.69
CGNG P inhibitory errors	-0.12 (0.17)	0.48
BART Responses per Balloon	0.17 (0.16)	0.30
Gender	0.41 (0.30)	0.18

Note: Gender = Male vs Female. Estimates are of log odds-like ratios of the probability of smoking group membership, relative to non-smokers.

Table 3.8: Estimates of odds-like ratios (with 95% confidence intervals) for risk factors of trajectory group membership.

Group Membership	Odds-Like Ratio		95% CI	P-Value
Decreasing vs. Non-Smokers	NU	1.21	0.82 – 1.79	0.36
	PRE	1.16	0.75 – 1.79	0.5
	SS	0.97	0.66 – 1.43	0.88
	ALC	**1.67**	**1.22 – 2.28**	**<0.001**
	MALE	1.00	0.48 – 2.06	0.99
Late-Escalating vs. Non-Smokers	NU	1.14	0.65 – 2.01	0.65
	PRE	1.00	0.54 – 1.84	0.98
	SS	**2.27**	**1.16 – 4.42**	**0.02**
	ALC	0.90	0.27 – 1.26	0.17
	MALE	**4.43**	**1.15 – 17.16**	**0.03**
High Stable vs. Non-Smokers	**NU**	**2.27**	**1.56 – 3.29**	**<0.001**
	PRE	1.32	0.89 – 1.96	0.15
	SS	1.26	0.87 – 1.83	0.22
	ALC	**1.70**	**1.24 – 2.32**	**<0.001**
	MALE	1.14	0.57 – 2.26	0.71
High Stable vs. Late-Escalating Smokers	**NU**	**1.99**	**1.04 – 3.81**	**0.03**
	PRE	1.32	0.67 – 2.63	0.42
	SS	0.55	0.26 – 1.17	0.12
	ALC	**2.92**	**1.31 – 6.51**	**<0.01**
	MALE	0.26	0.06 – 1.12	0.07

Note: NU = negative urgency, SS = sensation seeking, PRE = lack of premeditation, ALC = average alcohol use (drinks per week) during wave 1. Non-smokers were the reference group for the first three comparisons. Late-escalating smokers were the reference group in the fourth comparison.

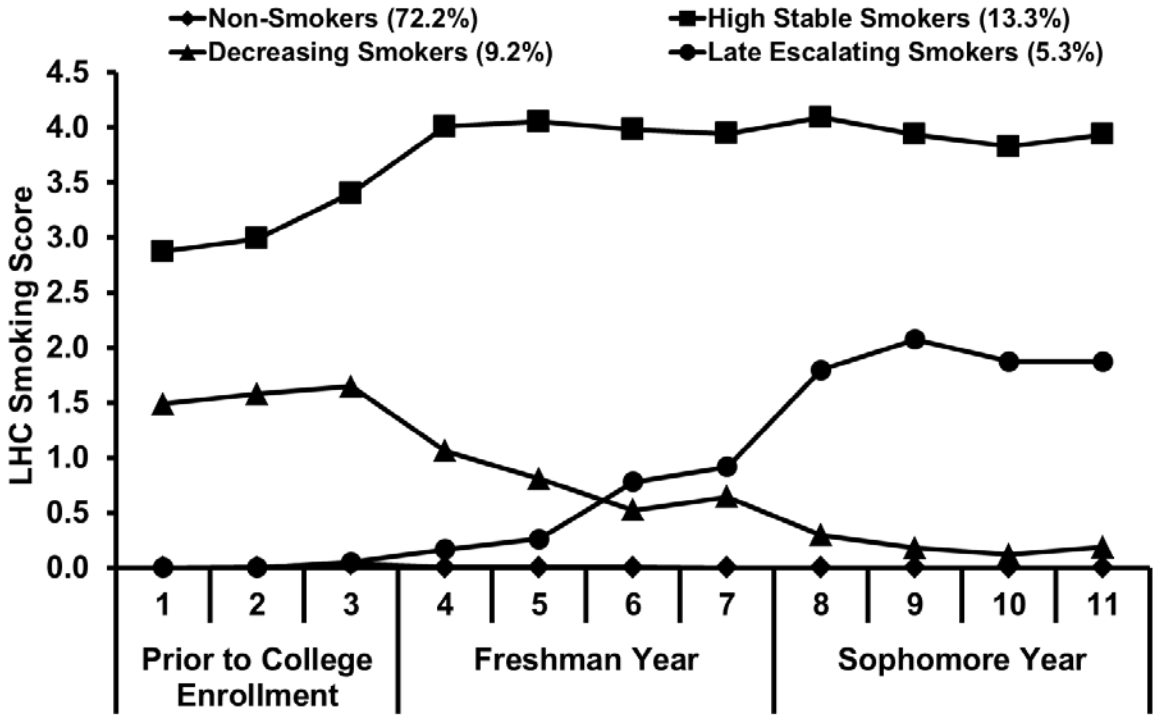

Figure 3.1: Trajectories of cigarette smoking frequency.

Time-points 1-3 are from the first wave of data and are comprised of 4-month blocks, and data from waves 2 and 3 (time-points 4-11) are comprised of 3-month blocks that corresponded approximately to the first and second years of enrollment at the university. Cigarette smoking frequency was assessed on a 0-5 scale using the LHC, with 0 = no smoking, 1 = once per month, 2 = once per week, 3 = 2-3 times per week, 4 = 4-5 times per week, and 5 = daily.

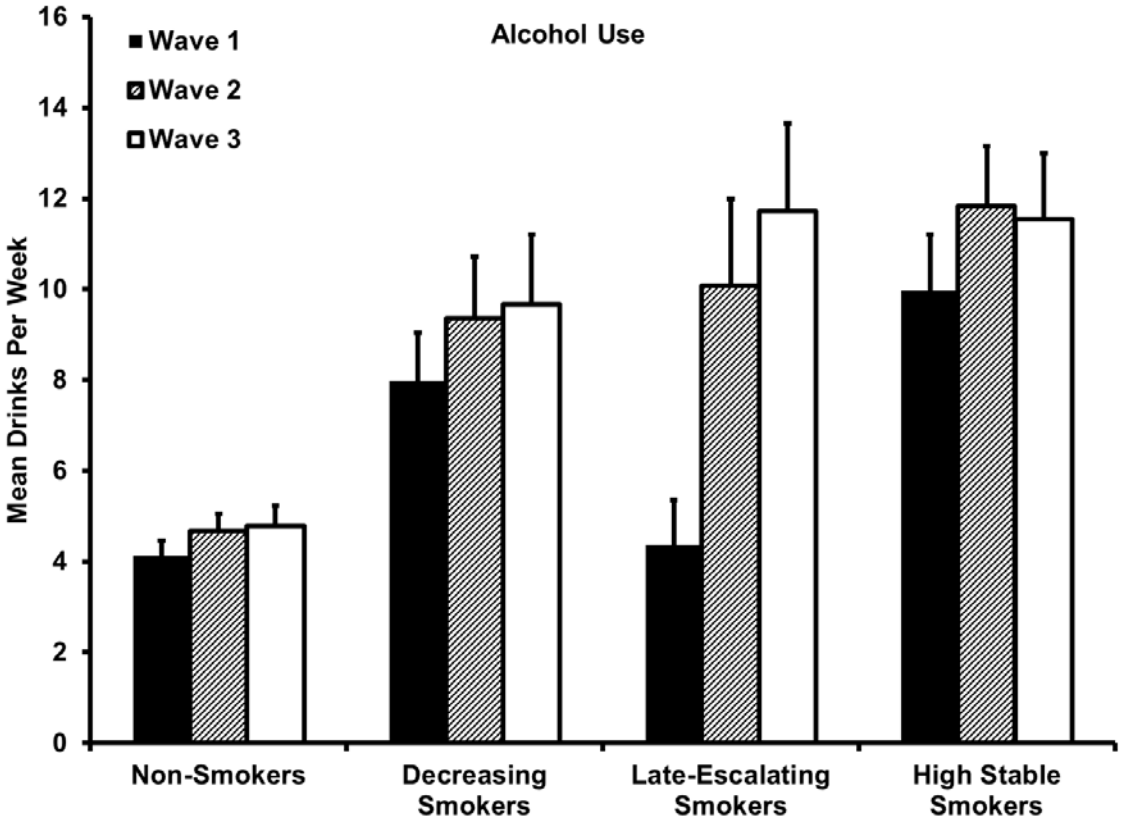

Figure 3.2: Mean alcohol use (drinks per week) at each yearly assessment for each trajectory group.

Error bars represent 1 SE.

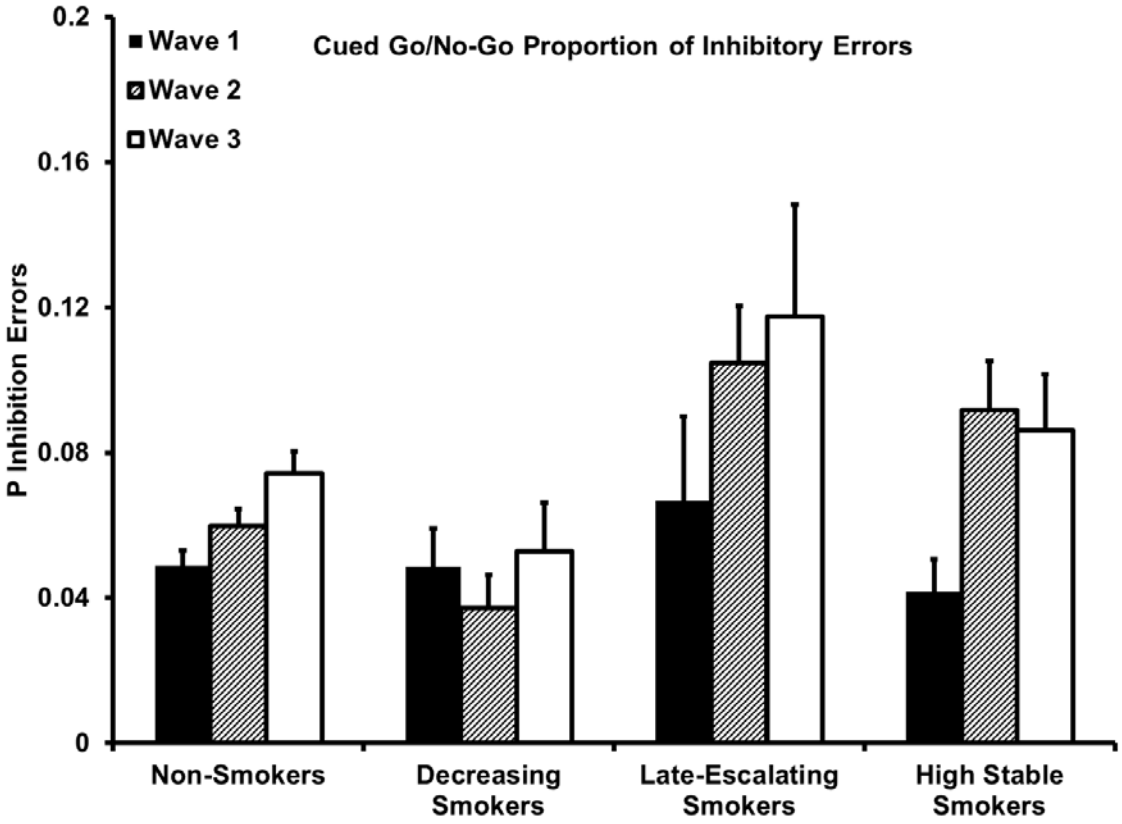

Figure 3.3: Proportion of inhibition errors on the cued-go/no-go task at each yearly assessment for each trajectory group.

Error bars represent 1 SE.

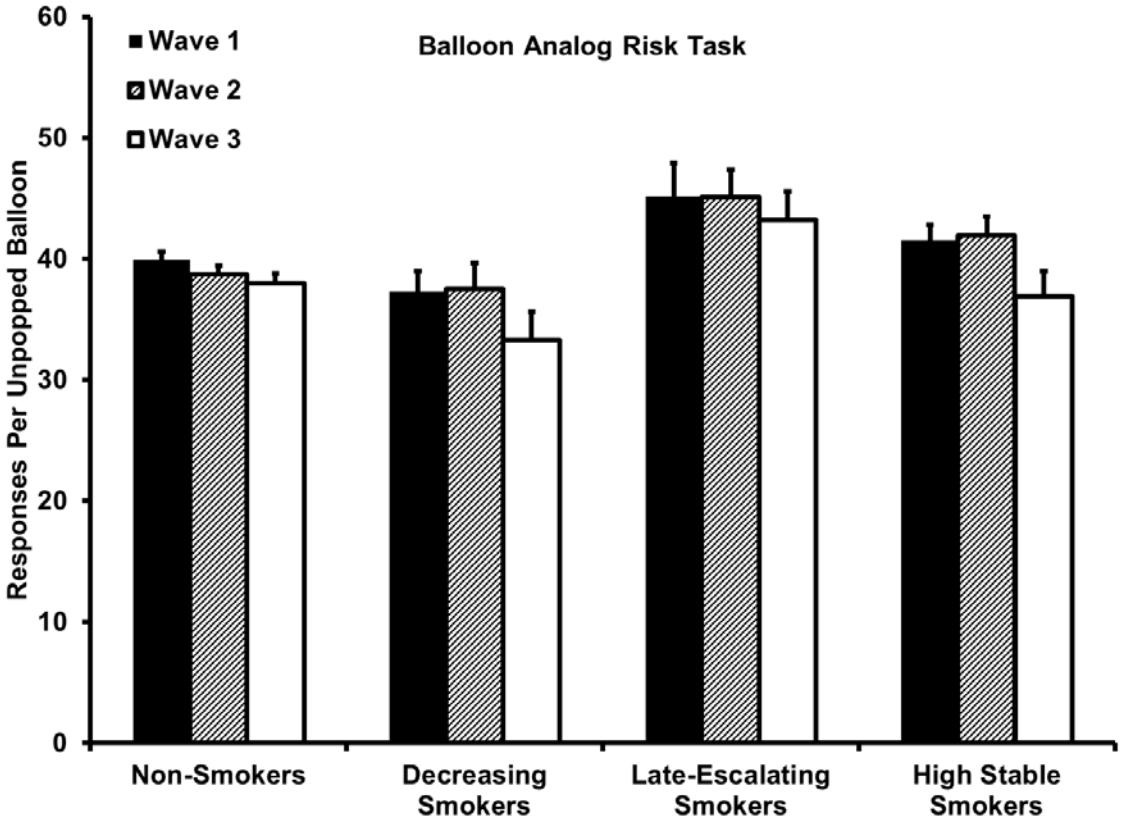

Figure 3.4: Responses per unpopped balloon on the BART at each yearly assessment for each trajectory group.

Error bars represent 1 SE.

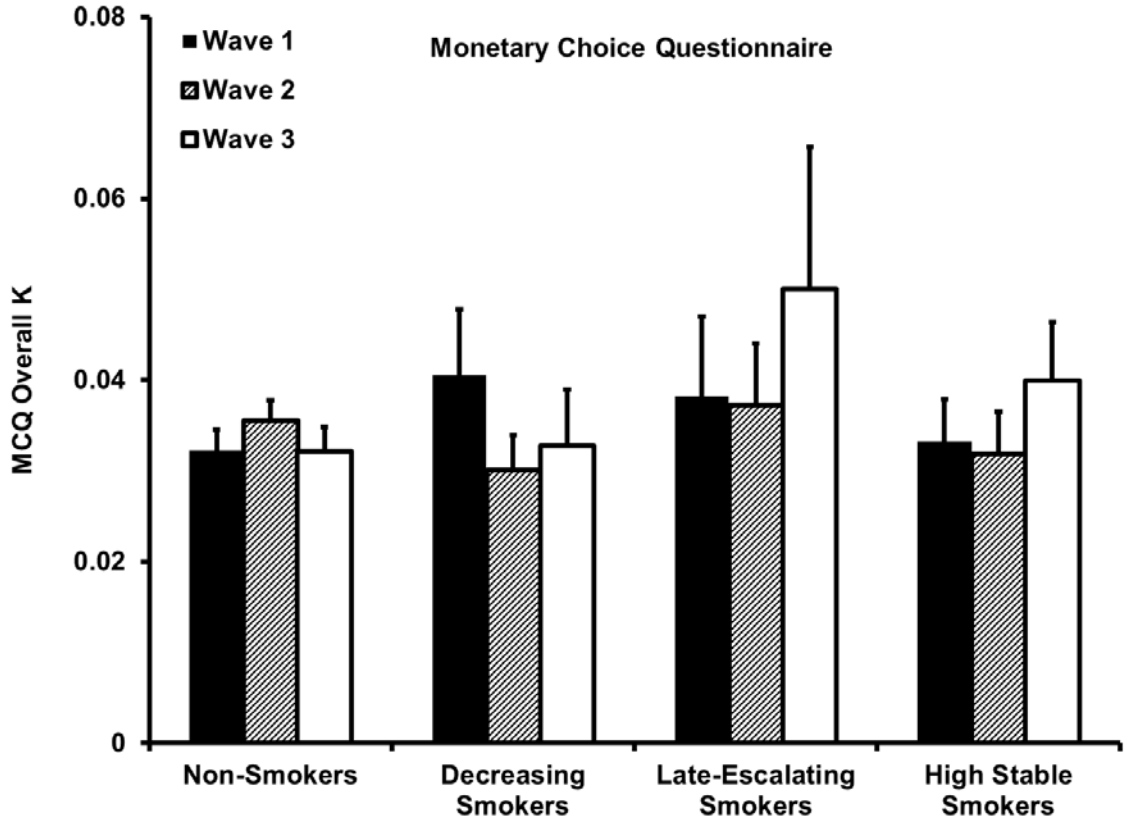

Figure 3.5: Mean overall K values at each yearly assessment for each trajectory group

Error bars represent 1 SE.

Chapter Four: Study 3 - Acute Effect of Alcohol on Inhibitory Control and Subsequent Tobacco Use in Young Adult Occasional Smokers

Introduction

Alcohol use has been widely reported as a risk factor for acute and long-term increases in tobacco use. Results from studies 1 and 2 demonstrated that alcohol use is associated with frequency of tobacco smoking on entrance to college and escalation of tobacco use in young adult college students across a three year period, even when controlling for impulsivity, which is consistent with research indicating that there is a strong association between alcohol use and tobacco smoking (Dierker et al., 2006; Harrison et al., 2008; Jackson et al., 2005; Shiffman et al., 2012; Weitzman & Chen, 2005). Cross-sectional and event-related studies have further confirmed this association by demonstrating that alcohol use accounts for a significant proportion of smoking occurrences and quantity of tobacco smoked in non-daily smokers (Jackson et al., 2010; Krukowski et al., 2005; Shiffman & Paty, 2006). Frequent pairings of alcohol with cigarette smoking may lead to greater symptoms of tobacco dependence as a result of alcohol-induced increases in exposure to the reinforcing effects of nicotine, the primary psychoactive component of tobacco. Thus, identifying the underlying mechanism(s) responsible for alcohol-induced increases in cigarette smoking is important in order to better understand the effect of alcohol on cigarette smoking and to aid in prevention and treatment efforts for those at risk of tobacco dependence.

Laboratory studies that have examined the relationship between alcohol and tobacco use have consistently found that acute alcohol increases smoking behavior, but the mechanisms associated with concurrent alcohol and tobacco use remains to be elucidated. For example, alcohol administration increases craving for the positive reinforcing effects of tobacco (Epstein, Sher, Young, & King, 2007; King & Epstein, 2005), the positive subjective effects of smoking (McKee et al., 2004; 2010), and tobacco self-administration (Barrett et al., 2013; King et al., 2009; McKee et al., 2010). However, this does not appear to be the result of a pharmacological interaction between nicotine and alcohol alone. Nicotine administration does not decrease the effect of alcohol on tobacco craving (McKee, O'Malley, Shi, Mase, & Krishnan-Sarin, 2008; Perkins et al., 2005), and acute alcohol does not increase subsequent intranasal nicotine administration (Perkins et al., 2005). Moreover, alcohol increases the positive subjective effects and self-administration of both denicotinized and nicotinized cigarettes (Barrett et al., 2013; King et al., 2009; McKee et al., 2004; 2010), suggesting that other mechanisms are responsible for the effect of alcohol on smoking.

Considerable evidence has indicated that dimensions of impulsivity are risk factors for tobacco use initiation and escalation. Studies 1 and 2 demonstrated that multiple dimensions of impulsivity (i.e. sensation seeking, negative urgency, and lack of premeditation) increase risk for initiation and frequent tobacco use in young adults. While trait measures of impulsivity are associated with risk for tobacco use initiation and escalation, it is also possible

that behavioral mechanisms of impulsivity, such as inhibitory control, are associated with alcohol-related increases in tobacco use. Inhibitory control is characterized as the ability to inhibit or suppress an inappropriate action or behavior, and is integral for controlling behavioral responses to internal and external stimuli such as cues signaling the availability of a drug. Multiple studies have demonstrated that inhibitory control as measured by cued go/no-go and stop signal tasks is impaired following consumption of alcohol (e.g. Marczinski & Fillmore, 2003; Dougherty et al., 2008; Fillmore et al., 2009). Moreover, the acute effect of alcohol on inhibitory control operates independently of trait measures of impulsivity. Fillmore et al. (2009) found that alcohol increased impairments in inhibitory control in individuals who are low and high in trait dimensions of impulsive-sensation seeking. While high sensation-seekers had higher baseline rates of inhibition errors, acute alcohol increased inhibition errors similarly in both groups, suggesting that inhibitory control may be a potential dimension of impulsivity that can be temporarily altered by acute alcohol consumption in a manner that is independent of trait dimensions of impulsivity.

Evidence also indicates that acute alcohol-related impairments in inhibitory control predict subsequent increases in drug consumption. Weafer and Fillmore (2008) examined the influence of alcohol-related impairments in inhibitory control on subsequent alcohol self-administration. Participants completed two sessions during which inhibitory control was examined following administration of placebo or a moderate dose of alcohol (0.65 g/kg). In a third session, participants were allowed to self-administer alcohol ad-libitum. Results

indicated that individual differences in the magnitude of alcohol-induced impairments in inhibitory control predicted subsequent alcohol self-administration. Specifically, individuals that demonstrated a greater magnitude of alcohol-induced impairment of inhibitory control consumed more alcohol during the subsequent ad-libitum self-administration session. Importantly, these differences were not attributable to baseline differences in inhibitory control or other trait measures of impulsivity, thus demonstrating a specific relationship between impairment of inhibitory control and subsequent alcohol use.

It is possible that alcohol's effect on inhibitory control may also influence cigarette smoking, but no study to date has investigated this potential relationship. Therefore, the objective of the current study is to examine alcohol-induced impairment of inhibitory control as a potential mechanism driving concurrent alcohol and tobacco use. Based on previous research, it was hypothesized that: 1) alcohol would increase ad-libitum cigarette smoking relative to placebo, 2) alcohol would also increase inhibition errors on a cued go/no-go task, and 3) the magnitude of alcohol-induced increases in inhibition errors would mediate the relationship between alcohol and increases in ad-libitum cigarette smoking behavior.

Method

Participants

Based on data from Weafer and Fillmore (2008), in which the correlation between inhibition errors and alcohol self-administration was 0.45, it was

estimated that a sample of size 37 would be sufficient for 80% power to detect an association of alcohol-induced inhibition errors with ad libitum smoking, assuming that the correlation between inhibition errors and ad libitum smoking would be similar to that between inhibition errors and alcohol intake.

Healthy young-adults completed a 3-session study that was approved by the University of Kentucky Medical Institutional Review Board. Participants were recruited through advertisements placed online (Craigslist), in newspapers (Kentucky Kernal, Lexington Herald-Leader), flyers placed around the University of Kentucky campus and in the local community, and through respondent driven sampling. Volunteers who were interested in participating in the study completed a brief internet-based questionnaire addressing general medical and legal issues, and current drug use. Those between the ages of 21-25 who reported good health, as well as non-daily tobacco and alcohol use, were invited to participate in the study.

During an orientation and medical screening day, volunteers completed a battery of medical and psychological questionnaires. Alcohol and tobacco use were verified by a Life History Calendar (LHC – Caspi et al., 1996) and a Timeline Followback Questionnaire (TLFB; Sobell, Maisto, Sobell, & Cooper, 1979; Sobell & Sobell, 1992). The TLFB also included inquiries about preferences for tobacco type (i.e. mentholated or non-mentholated tobacco), brand, and tobacco purchase history. Volunteers practiced the experimental performance tasks until performance was consistent and accurate across consecutive trials. To be eligible to participate, participants had to report current

occasional cigarette smoking in the past month (with reported smoking < five days per week and < 20 cigarettes per week over the past three months (with similar patterns and no daily smoking within the previous two-year period), and current alcohol consumption (an average of one or more occasions of alcohol consumption per week, and at least three drinks on one occasion within the past 30 days; Fillmore et al., 2009). Participants were excluded if they were tobacco dependent (Fagerstrom Test of Nicotine Dependence scores >4; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991); alcohol dependent (as determined based on the SCID), or had a history of and/or current significant physical or mental illness (i.e. cardiovascular disease, neurological or psychiatric disorder); regular use of other centrally-active drugs; or pregnant or breastfeeding. All participants were screened and approved by a study physician prior to enrollment.

Design

A randomized, single blind, placebo-controlled, within-subjects design was used to examine the effect of alcohol on behavioral inhibition and subsequent ad-libitum cigarette smoking.

Study Drugs

Alcohol: Alcohol administration was similar to dosing procedures described in Fillmore et al. (2009). Alcohol doses contained either 0.0 (i.e., placebo) or 0.65 g/kg alcohol, and were calculated based upon body weight. The

alcohol beverage consisted of one part alcohol and three parts carbonated mix, divided equally into two glasses. Participants were given two minutes to finish each glass, and the two glasses were served four minutes apart. The placebo beverage consisted of four parts carbonated mix and was served in the same manner. Three milliliters of alcohol was floated on the top of each glass, and the glasses were sprayed with an alcoholic mist, which resembled condensation and provided a strong alcohol odor. Previous research has shown that individuals report that these beverages contain alcohol (e.g., Fillmore & Blackburn, 2002). The 0.65-g/kg dose produces an average peak BAC between 75 - 80 mg/100 mL and was chosen on the basis of previous research that showed that response inhibition is reliably impaired at this BAC (Marczinski & Fillmore, 2003; Weafer & Fillmore, 2008; Fillmore et al., 2009). The peak BAC was expected to occur approximately 60 min after drinking (Fillmore & Vogel-Sprott, 1998).

Tobacco: Participants had free access to their preferred-brand filtered cigarettes during the ad-libitum smoking session.

Experimental Measures

Ad-libitum smoking puff topography: Smoking topography was measured by placing cigarettes in a mouthpiece connected at the front and rear with PCV tubing attached to a volumetric transducer. The flow of air through the mouthpiece was measured to determine the duration and volume of each puff (e.g., Lee, Perkins, Zimmerman, Robbins, & Kelly, 2011). Smoking topography measures during the three-hour smoking period included number of cigarettes

smoked, latency to first cigarette, puffs per cigarette, and total puff volume and duration.

Behavioral Assessments

Inhibitory Control

A cued go/no-go task was used as the measure of behavioral inhibition (see Study 2 for task details). Previous research has indicated that performance on the task is sensitive to acute alcohol administration (e.g. Weafer & Fillmore, 2008).

Psychomotor Performance

A Digit Symbol Substitution Task (DSST; McLeod, Griffiths, Bigelow, & Yingling, 1982) was used as a control measure of general psychomotor performance. Participants used a numeric keypad to enter a geometric pattern associated with one of the 9 digits displayed on a computer monitor. Dependent measures were number of correct and incorrect patterns. This task was completed in 90 seconds (~60 trials). Previous research has indicated that performance on the DSST is sensitive to acute alcohol administration (e.g. Rush, Higgins, Hughes, Bickel, & Wiegner, 1989).

Supplementary Questionnaires

Questionnaire of Smoking Urges - Brief (QSU-B; Cox, Tiffany, & Christen, 2001). The QSU-B is a 10-item questionnaire that consists of two factor-derived subscales (Factor 1: desire and intention to smoke, with smoking perceived as

rewarding; Factor 2: anticipation of relief from negative affect with an urgent desire to smoke) developed to assess smoking urge. Participants rated items on a 100-unit line from “strongly disagree” to “strongly agree.”

Biphasic Alcohol Effects Scale (BAES; Martin, Earleywine, Musty, Perrine, & Swift, 1993). The BAES is a 14-item adjective rating scale that is divided into two 7-item subscales designed to assess the stimulant and sedative effects of alcohol (Stimulation: elated, energized, excited, stimulated, talkative, up, and vigorous; Sedation: difficulty concentrating, down, heavy head, inactive, sedated, slow thoughts, and sluggish). Participants rated items on an eleven-point scale (0 – 10) based upon the extent to which alcohol produced the effect described by the adjective from “not at all” to “extremely.”

Procedure

Following the orientation and medical screening session, participants completed three study sessions, each of which was approximately 5 hours in duration. Each session was similar in structure, with the only exception being the dose of alcohol received. The first session was a practice session and subjects were given placebo alcohol, but participants were not informed that placebo was administered. The practice session was used to familiarize the subject with the experimental procedures and performance tasks. Alcohol dose (0.0 or 0.65 g/kg) was randomized across the second and third session for each subject. Sessions were scheduled a minimum of 48 hours apart. Subjects were instructed to abstain from solid food and caffeine for 4 h, and tobacco and alcohol use for 12 h

before each experimental session. Upon arrival, breath-alcohol, expired CO, and urine samples for testing drug use and pregnancy status were collected, and a brief field sobriety test was administered. An expired air sample positive for alcohol or tobacco (CO > 5) or a urine sample positive for other drug use triggered the rescheduling of a session. Subjects were provided with a low-fat and caffeine-free snack consisting of two Kellogg's Nutri-Grain ® cereal bars and a 6.75-ounce fruit juice after arrival to provide standardized GI and nutritional conditions. Participants consumed the snack immediately before the pre-dose experimental measures, which was approximately twenty minutes prior to alcohol administration.

Subjects completed experimental measures 30 min after arrival (i.e., baseline measures, see Table 4.1). Measures were administered in a fixed order (i.e. QSU, BAES, cued go/no-go, DSST) and were completed in approximately 18 minutes. Alcohol administration occurred immediately following the baseline assessment. Experimental measures were collected again 30 minutes post alcohol consumption. Immediately following task completion, participants were allowed ad-libitum access to their preferred-brand of cigarettes for 3 hours. All cigarettes were smoked using the puff topography device. BAC and subjective questionnaires were taken 30-minute intervals post-alcohol administration. Participants were required to remain in the study room during the ad-libitum tobacco access period but had free access to non-caffeinated beverages and entertainment options, including books, games and movies. At the end of each session, subjects completed the field sobriety and BAC tests again. Subjects

were released once they completed the field sobriety test in the same manner as when they arrived in the morning, and had a BAC $\leq$ 20 mg/100 mL. Subjects were compensated for their time ($185: $25 for medical screening, $40 per session, and a one-time $40 completion bonus paid at the end of the final session).

Data Analysis

A 2-factor (Alcohol Dose x Time) within-subject mixed-models ANOVA examined the effect of alcohol on performance measures and subjective questionnaires, and t-tests examined the effect of alcohol on cigarettes smoked and smoking puff topography. Follow-up testing on main effects and interactions were conducted using simple effects models and Tukey-Kramer adjusted differences of least-squared means. A mediation approach (e.g. Baron & Kenny, 1986) using linear mixed modeling tested the hypothesis that alcohol-induced changes in performance (e.g., inhibition errors) would mediate the relationship between alcohol and increases in ad-libitum cigarette smoking. Supplementary correlations examined the relationship between UPPS impulsivity dimensions and alcohol-induced changes ad-libitum smoking. All statistics were considered significant at $p \leq .05$.

Results

Sample Characteristics

Thirty-six volunteers initiated the study; nine participants were excluded from the study following the medical screening (four participants did not meet the inclusion criteria for tobacco use, four participants met exclusionary criteria for drug or alcohol dependence, and one participant was excluded due to a current mental disorder). Four participants dropped out for reasons unrelated to the study. An interim analysis indicated that correlations between alcohol-induced inhibition errors and ad libitum smoking were much smaller than estimated (the highest correlation between alcohol-induced inhibition errors and change in average volume per cigarette was 0.07) mandating a substantially larger sample size (n=1600) would be needed to detect the small emerging relationship. Based on feasibility limitations and the modest clinical significance of the emerging effect, a decision was made to terminate the study with a final sample size of 23. Sample characteristics are presented in Table 4.1. Participants reported drinking alcohol and smoking cigarettes approximately twice a week, and reported drinking an average of five drinks and smoking two cigarettes per occasion. Participants were not nicotine dependent (FTND = 0).

Blood-Alcohol Concentrations

Figure 4.1 displays the mean blood-alcohol concentration curve. No detectable alcohol concentrations were obtained during the placebo session. Mean peak BAC was 66.3 mg/100 mL (SD = 8.30). An ANOVA examined the

time course of the BAC curve. There was an effect of time [F(8,168) = 288.63, p<.001], with BAC rising as a function of alcohol, then descending starting at 90 minutes post-dose.

Effect of Alcohol on Tobacco Smoking

Sixteen out of twenty-three participants smoked tobacco during the free-access interval during placebo sessions, compared to twenty out of twenty-three during the alcohol sessions. The average number of cigarettes smoked increased during alcohol sessions, but this measure did not reach statistical significance (p = 0.08). Table 4.3 displays the effect of alcohol on cigarettes smoked and ad-libitum smoking puff topography. T-test results revealed that alcohol increased average volume and time per cigarette smoked while decreasing latency to smoke (p<0.05).

Inhibitory Control

Figure 4.2 displays proportion of inhibition errors to go targets following go cues (left panel) and no-go cues (right panel) on the cued go/no-go task. There was a main effect of time for proportion of inhibition errors following go cues [F(1,22) = 21.94, p<.001] and no-go cues [F(1,22) = 8.11, p<.01], with inhibition errors increasing post-dose for both cue conditions, but these changes were unrelated to alcohol. There were no main effects and/or interactions on reaction time to go targets following go cues or no go cues.

Psychomotor Performance

Figure 4.3 displays alcohol effects on correct (left panel) and incorrect (right panel) trial rates on the DSST. There was a significant dose by time interaction on correct trials [F(1,22) = 4.15, p=.05]. Follow up testing indicated that correct trials decreased following the active alcohol dose, relative to placebo. A main effect of time on incorrect trials was trending toward significance [F(1,22) = 3.97, p=.06]; small magnitude increases in incorrect trial rates were observed post-dose, but these changes were unrelated to alcohol.

Mediation Analyses

A mediation analysis was conducted to examine whether inhibition errors on the cued go/no-go task mediated the relationship between alcohol and tobacco smoking. A path diagram for the mediation analysis is presented in Figure 4.4. A series of four linear mixed models assessed whether: alcohol predicted ad libitum smoking (direct effect; path c), alcohol predicted inhibition errors (path a), inhibition errors predicted ad libitum smoking (path b), and whether the relationship between alcohol on tobacco was altered when inhibition errors were included as a predictor (path c'). Smoking puff topography measures considered in the model were average time and average volume per cigarette (chosen based upon significant t-tests in the main effects analysis). Cued go/no-go measures considered in the model were post-dose assessments of proportion of inhibition errors. Results from analyses using average time and average volume were comparable (data not presented). Effect sizes were calculated by

dividing the absolute value of the estimated coefficient for each predictor variable by the square root of the estimated residual variance, which produces an effect size analogous to Cohen's d. Resulting effect sizes were interpreted using Cohen's d conventions for small ($\geq$.20) medium ($\geq$.50), and large ($\geq$.80) effect sizes (Cohen, 1988).

The effect of alcohol on average volume (Path c) was significant [$F(1,22) = 4.81$, $p<.05$; $d = 0.64$], confirming the t-test results indicating that alcohol increased average volume per cigarette. The effect of alcohol on proportion of inhibitory errors (Path a) was not significant [$F(1,22) = 2.65$, $p =0.12$, $d = 0.48$]. Since alcohol failed to predict increases in proportion of inhibitory errors, no mediation could be detected. Nonetheless, the results and associated statistical information are presented below to further clarify the strength of the relationship between variables. The effect of proportion of inhibition errors on average volume (Path b) was also not significant [$F(1,22) = 2.13$, $p = 0.16$; $d = 0.29$]. The final step (Path c') indicated that the direct effect of alcohol on average volume retained significance when proportion of inhibition errors were controlled [$F(1,21) = 5.71$, $p<.05$; $d = 0.71$]. However, proportion of inhibition errors did not increase average volume when alcohol dose was controlled [$F(1,21) = 2.96$, $p=0.10$; $d = 0.36$]. Figure 4.5 (left panel) presents a scatterplot of the relationship between change in inhibition errors and average volume per cigarette (with change being the difference between post-dose alcohol and placebo assessments). The effect size for proportion of inhibition errors predicting an increase in smoking behavior when alcohol was controlled was small (0.36), which confirms the interim

analysis finding of a small correlation (0.07) between alcohol-induced inhibition errors and change in average volume per cigarette.

A second mediation model was conducted replacing cued go/no-go inhibition errors with DSST correct trials. The effect of alcohol on correct trials (path a) and correct trials on average volume (path b) were significant (Path a: $F(1,22) = 5.88$, $p<.05$; $d = 0.71$, Path b: $F(1,22) = 12.75$, $p<.01$; $d = 0.71$). When correct trials were included in the model with alcohol (path c'), results indicated that alcohol was no longer significant [$F(1,21) = 1.51$, $p=0.23$, $d= 0.39$] but correct trials was significant [$F(1,21) = 9.06$, $p<.01$; $d = 0.65$], thus identifying DSST correct trials as a mediator of the relationship between alcohol and smoking puff topography. A scatterplot presenting this relationship shows that individuals who show greater deficits in accuracy on the DSST smoke more in response to the acute effect of alcohol (Figure 4.5, right panel).

Supplementary Analysis

Subjective Effects of Alcohol and Tobacco Craving

A supplemental analysis was conducted to examine the effect of alcohol on tobacco craving and subjective reports of stimulation and sedation (Figure 4.6). A significant interaction of alcohol and time was found on QSU Factor 1 (Panel A, Positive Effects) [$F(2,44) = 7.38$, $p<.001$]. Simple effects analyses indicated that alcohol increased desire to smoke for the positive effects of tobacco at thirty minutes post-dose, relative to placebo. No other alcohol effects were found. Main effects of time were found on QSU Factor 2 (Panel B) [F(2,44)

= 8.32, p<.01] and BAES Sedation (Panel C) [F(2,44) = 13.00, p<.001] with both measures increasing at 30 and 60 minutes relative to baseline, unrelated to alcohol dose. There was a dose by time interaction on BAES stimulation (Panel D) [F(2,44) = 12.60, p<.001]. However, follow-up testing indicated that this effect was reflected to baseline difference between placebo and the active days.

Correlational Analysis

A correlational analysis examining the relationship between UPPS-P dimensions and alcohol's effect on ad-libitum smoking found no relationships between dimensions impulsivity and alcohol-related alterations in ad-libitum smoking behavior.

Discussion

The primary objective of this study was to determine whether alcohol-induced impairments in inhibitory control mediated the relationship between acute alcohol consumption and increases in ad libitum tobacco use. As anticipated, alcohol increased ad-libitum smoking behavior. However, assessments of cued go/no-go performance found that alcohol did not significantly increase the magnitude of inhibition errors to a greater extent than placebo administration. Furthermore, alcohol's effect on inhibitory control did not mediate the relationship between alcohol consumption and subsequent increases in smoking behavior. However, alcohol impaired DSST performance, indicating that a pharmacologically active dose was administered. Dose-related

effects were also detected on subject-reported craving for the positive reinforcing effects of tobacco (QSU Factor 1). Furthermore, alcohol impairment of DSST performance mediated the effects of alcohol on cigarette smoking, indicating that the study design was effective in engendering performance-based mediation of alcohol's effects on smoking. These results provide compelling evidence that mechanisms other than acute-alcohol impairment of inhibitory control, as measured by the Go/No Go Task, mediate the relationship between concurrent alcohol and tobacco use.

The finding that acute alcohol consumption increased ad-libitum smoking behavior in this study is consistent with results from previous laboratory studies (Barrett et al., 2013; King et al., 2009; McKee et al., 2010), and provides further confirmation of cross-sectional and event-related studies that have established a link between alcohol and increased cigarette smoking in non-daily smokers (i.e. Dierker et al., 2006; Harrison & McKee, 2008; Jackson et al., 2005; 2010; Krukowski et al., 2005; Shiffman & Paty, 2006; Shiffman et al., 2012; Weitzman & Chen, 2005). While the change in the number of cigarettes smoked following placebo versus alcohol administration was only marginally significant, average time and volume per cigarette smoked significantly increased, and latency to smoke decreased, indicating that participants started smoking earlier during the ad-lib access period and consumed more tobacco per cigarette while under the influence of alcohol. These results further confirm alcohol use as a risk factor for situational increases in tobacco use in non-dependent smokers.

The results of this study did not confirm the hypothesis that acute alcohol impairment of inhibitory control is a mechanism that mediates the relationship between alcohol consumption and smoking. It is important to note that alcohol did not significantly increase the overall magnitude of inhibition errors on the cued go/no-go task above those found after placebo administration, which is inconsistent with previous research (e.g. Marczinski & Fillmore, 2003; Dougherty et al., 2008; Fillmore et al., 2009), and could be a potential explanation for the lack of a mediation effect.

There are a number of potential explanations for the absence of alcohol effects on the cued go/no-go task relative to placebo. As displayed in figure 4.2 (left panel) inhibition errors were increased post-dose following both placebo and alcohol relative to pre-dose baseline performance, which suggests that fatigue or boredom could be influencing these data, thereby diminishing the sensitivity of task performance to alcohol effects. Previous studies reporting an effect of alcohol on inhibition errors collected cued go/no-go performance only post-dose (e.g. Marczinski & Fillmore, 2003; Weafer & Fillmore, 2008), and including pre-dose assessments in the current study may have increased inhibition errors related to fatigue or boredom. However at least one study (Fillmore et al., 2009) assessed the effects of multiple doses of alcohol on comparable cued go/no-go task performance at baseline and two separate times post-dose and found a consistent effect of alcohol on inhibition errors above those found following placebo administration, which is inconsistent with the hypothesis that fatigue or

boredom was the main factor differentiating the current study from previous studies in which alcohol-induced increases in inhibitory errors were reported.

It is also possible that the results found in this study were due to increased sensitivity to the learned associations between the cue/target manipulations during the course of the study. However, evidence from the current study and previous research do not support this potential explanation. Fillmore et al. (2009) tested three different dose conditions (0.0 g/kg, 0.45 g/kg, and 0.65 g/kg) each on two occasions, and did not find a significant dose replication effect, suggesting that alcohol's effects were stable across sessions and unrelated to degree of subject practice/experience with the task. Furthermore, a supplemental analysis of a dose order effect was not significant (data not presented), providing evidence against a potential increase in the sensitivity to alcohol effects based on the amount of practice/experience with the cued go/no-go cue/target manipulations. The lack of a significant effect of dose order is also inconsistent with an expectancy effect as a potential explanation for the comparable inhibition error rates following placebo and alcohol. In fact, a previous study of expectancy effects on cued go/no go task performance indicated that expectancy of alcohol actually improves inhibitory control relative to a no-alcohol condition – a result opposite those obtained during placebo sessions in the present study (Marczinski & Fillmore, 2005).

Gender differences have been found in previous research examining alcohol impairment of inhibitory control (e.g. Fillmore & Weafer, 2004). Gender could have been a potential factor in the discrepancy between the current study

and previous studies that have found an overall effect of alcohol on impairment of inhibitory control. In the present study, 65% of the subjects were male. Results from a supplemental analysis examining the effects of gender as a between-subjects factor indicated a significant Gender x Dose x Time interaction on proportion of inhibition errors [Figure 4.7; $F(1,21) = 5.14$, $p<.05$]. Simple effects tests revealed that post-dose assessment of inhibition errors differed as a function of gender and dose, with males showing increased inhibition errors following alcohol relative to placebo while females showed comparable increases in inhibition errors following both placebo and alcohol administration. Furthermore, females had fewer inhibition errors than males at pre-dose assessments. An analysis of reaction time to go targets also revealed a significant Gender x Time interaction [Figure 4.8; $F(1,21) = 5.98$, $p<.05$]. Simple effects indicated that reaction time to go targets decreased from pre- to post-dose for females, but not males. Furthermore, females had longer reaction times than males at both pre- and post-dose assessments. Taken together, these results indicated that males had shorter reaction times and higher baseline rates of inhibition errors than females, and inhibition errors increased following alcohol consumption in males only.

An additional mediation analysis was conducted to determine whether acute alcohol impairment of inhibitory control mediated the relationship between alcohol consumption and increases in tobacco use in males alone. While the direct effect of alcohol on smoking behavior remained significant, proportion of inhibition errors did not predict smoking behavior, indicating that alcohol

impairment of inhibitory control did not mediate the relationship between alcohol and smoking behavior in males alone. Finally, additional analyses including gender were conducted on DSST and subjective measures with results indicating that there were no differences related to gender and dose. Thus, gender differences were unique to those observed on cued go/no-go performance.

While the magnitude of alcohol impairment of inhibitory control did not mediate the relationship between alcohol and tobacco use, individual differences in alcohol impairment of DSST performance did mediate the relationship. Specifically, participants with fewer correct trials following alcohol (relative to placebo) had greater increases in smoking behavior after consuming alcohol. In a recent meta-analysis examining the performance-related effects of nicotine in non-smokers and non-deprived smokers, Heishman, Kleykamp, and Singleton (2010) found that nicotine increased performance in several cognitive domains, including components of fine motor performance, attention, and working memory, which suggests that alcohol-related increases in smoking behavior may be a compensatory response for those with a greater magnitude of alcohol-related decrements in cognitive performance. However, it is important to note that the DSST is sensitive to multiple aspects of cognitive performance, so pinpointing a specific component of cognitive function that may be driving alcohol-related increases in smoking behavior is speculative at this time. In addition, alcohol does not increase self-administration of nicotine alone (e.g. Perkins et al., 2005), which does not support the hypothesis that nicotine is compensating for alcohol-related decrements in cognitive performance and increasing concurrent use of

tobacco following alcohol consumption. Still, more research is needed to further examine the dose-related effects of nicotine on cognitive performance under the influence of alcohol using tasks with greater specificity to various aspects of cognitive performance, in order to determine whether alcohol-related decrements in particular components of cognitive performance may be responsible for subsequent increases in tobacco use.

Aside from mechanisms related to cognitive performance, it is also possible that alcohol use increases smoking behavior by altering the reinforcing effects of non-nicotine sensory components of tobacco smoke. Previous studies have found that non-dependent smokers who used alcohol and tobacco concurrently reported that alcohol increases the pleasurable effects of smoking while decreasing negative effects associated with tobacco (i.e. nausea; King et al., 2009; McKee et al., 2004; 2010). In addition, McKee et al. (2010) found that craving for the positive reinforcing effects of smoking increased after consumption of alcohol *and* a taste-masked placebo, which suggests that alcohol cues may provide a discriminative stimulus for smoking in individuals who frequently pair alcohol and tobacco use. However, subsequent increases in self-administration of tobacco occurred only following alcohol consumption suggesting that, while external cues associated with alcohol may increase craving for tobacco, the interoceptive effects of alcohol use are primarily responsible for subsequent increases in smoking behavior.

Peak BAC readings in this study were slightly lower (66.3 mg/100 mL) than has been reported in other studies using the same 0.65 g/kg dose of alcohol

(73.4 mg/100 mL; Fillmore et al., 2009). One potential explanation for this discrepancy is that participants consumed a low-fat snack (i.e. two Nutri-Grain ® bars and a 6.75 oz. fruit juice) approximately 20 minutes prior to alcohol consumption. This snack was provided to standardize GI function and decrease the potential aversive effects of the alcohol dose, but may have altered alcohol absorption. Although overall BAC dropped between 60 and 90 minutes post-dose, there was a substantial amount of individual variation in BAC at the 90-minute post-dose assessment. Thirteen out of twenty-three participants had breath alcohol levels that were comparable with BAC readings at 60 minutes post-dose (i.e. within 3 mg/100mL), suggesting that the pre-dose snack may have delayed absorption of alcohol in this study.

Limitations to the current study should be noted. First, the current sample included only subjects ages 21 and above, due to ethical restrictions on administering alcohol to individuals below the legal age limit for alcohol consumption. As a result, it was not possible to examine alcohol's effect on tobacco use in young adults between the ages of 18-20, which eliminated a potentially significant portion of young adult population who are in a critical period for risk of tobacco escalation. Second, only a single active dose of alcohol was administered in this study, which limited the ability to examine the dose-response effects of alcohol on inhibitory control and subsequent tobacco use. Results indicated that the 0.65 g/kg alcohol concentration increased smoking behavior in the sample of young adult occasional smokers, but it is unknown whether lower doses of alcohol would engender similar increases in smoking behavior, or

whether mediation effects of inhibitory errors on smoking would have been observed at other alcohol doses. Thus, additional research is needed using multiple doses of alcohol so the magnitude of changes in tobacco use and inhibitory errors can be measured at different BACs. Third, self-reported alcohol and tobacco use assessments were used to determine if participants met the inclusion criteria for tobacco and alcohol use in the study. Such assessments may be sensitive to recall bias (i.e. Shiffman, 2009a) so it is possible that there was some error in determining the eligibility of participants based upon self-reported use. Fourth, cigarette smoking during the ad-libitum sessions took place in a laboratory environment in the absence of any programmed constraints on smoking behavior. It is possible that the disinhibitory effects of alcohol would be more closely associated with changes in smoking behavior under conditions in which ad-libitum smoking was influenced by inhibitory factors. Future studies examining alcohol-induced changes in smoking behavior as a function of systematic changes in smoking constraints would be needed to address this possibility. Finally, it is important to note that the current study used a single task to examine alcohol-induced decrements in behavioral inhibition, so it is possible that other dimensions of behavioral inhibition not measured in this study are linked to alcohol-induced increases in cigarette smoking. Future research is needed using a broader range of behavioral inhibition measures to examine other dimensions of behavioral inhibition as potential mechanisms underlying the effects of concurrent alcohol and tobacco use.

Taken together, the results of this study support previous research indicating that acute alcohol consumption increases smoking behavior, but there is no evidence that alcohol-induced impairment of inhibitory control is a primary mechanism that accounts for concurrent alcohol and tobacco use. This suggests that other potential mechanisms are more likely to mediate the relationship between alcohol and tobacco use. Alcohol-induced impairment of performance on the DSST task was found to mediate the relationship. However, given that the DSST performance is highly sensitive to the effects of alcohol and other drugs, performance on this task could serve as a nonspecific marker of sensitivity to alcohol effects and thus serve as a marker of alcohol effects on other mechanisms. More research is needed to determine more specific dimensions of performance that may account for the alcohol-related increases in smoking behavior.

Table 4.1: Participant demographics and alcohol/tobacco use.

Demographic	Mean (SD)	Range
Age	22.4 (1.4)	21 – 25
Gender (% Female)	8 (35%)	
Smoking Characteristics		
Smoking days per week	2.0 (1.1)	0.5 – 4.5
Cigarettes per smoking day	2.2 (0.8)	1.0 – 4.0
FTND Score	0.0 (0.2)	0.0 – 1.0
Alcohol Use Characteristics		
Drinking days per week	2.3 (0.9)	0.6 – 4.1
Drinks per drinking day	5.0 (3.5)	2.5 – 14.7

Note: FTND – Fagerstrom Test for Nicotine Dependence

Table 4.2: Study 3 session timeline.

Time (min)	Procedure
- 60	Intake
- 30	Experimental Assessment
- 10	Begin alcohol (or placebo) admin
0	End alcohol (or placebo) admin
30	BAC, Questionnaire Measures
40	Performance Measures
60	BAC, Questionnaires – Begin ad-libitum smoking
90-240	BAC and questionnaires taken every 30 min
240	End ad-libitum smoking, BAC and Field-Sobriety Test

Table 4.3: Effect of alcohol on cigarettes smoked and smoking puff topography during the ad libitum smoking period.

Smoking Measure	0.0 g/kg	0.65 g/kg	t
	M (SE)	M (SE)	
# of Cigarettes	1.2 (0.2)	1.6 (0.2)$^{+}$	1.86
Average Puffs	11.8 (1.9)	14.4 (1.6)	1.29
Average Time (s)	16.9 (2.8)	21.8 (2.7)*	2.07
Average Volume (mL)	735.1 (120.7)	999.7 (124.2)*	2.14
Latency to smoke (min)	76.1 (15.9)	34.2 (12.9)*	-2.24

$^{+}$p = .08, *p<.05. t-test df = 22.

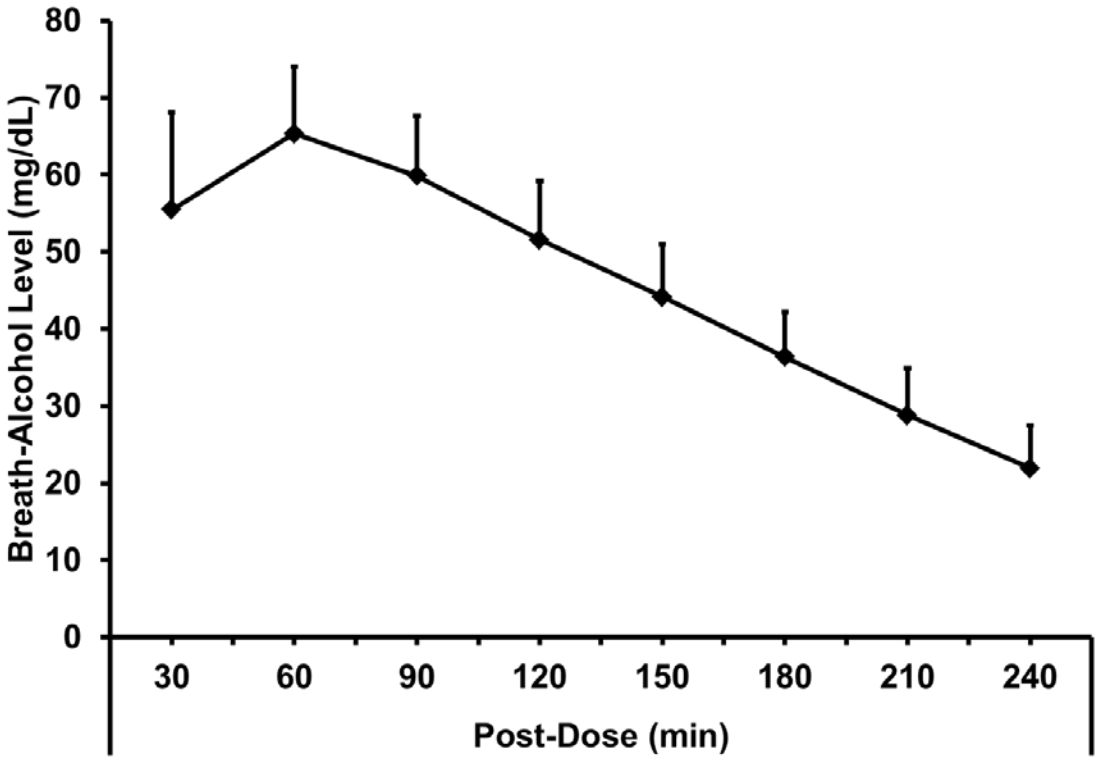

Figure 4.1: Breath alcohol concentrations (in mg/dL) during sessions following 0.65 g/kg dose administration.

Note: Errors bars represent 1 SD.

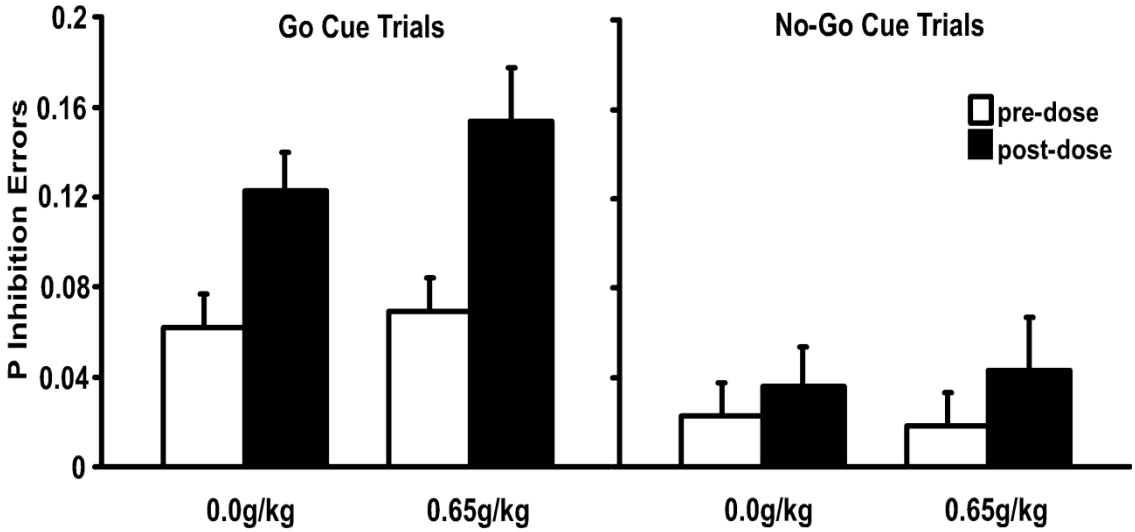

Figure 4.2: Effect of alcohol on proportion of inhibition errors to no go targets following go cues (Left) and no go cues (Right).

Note: Error bars represent 1 SE.

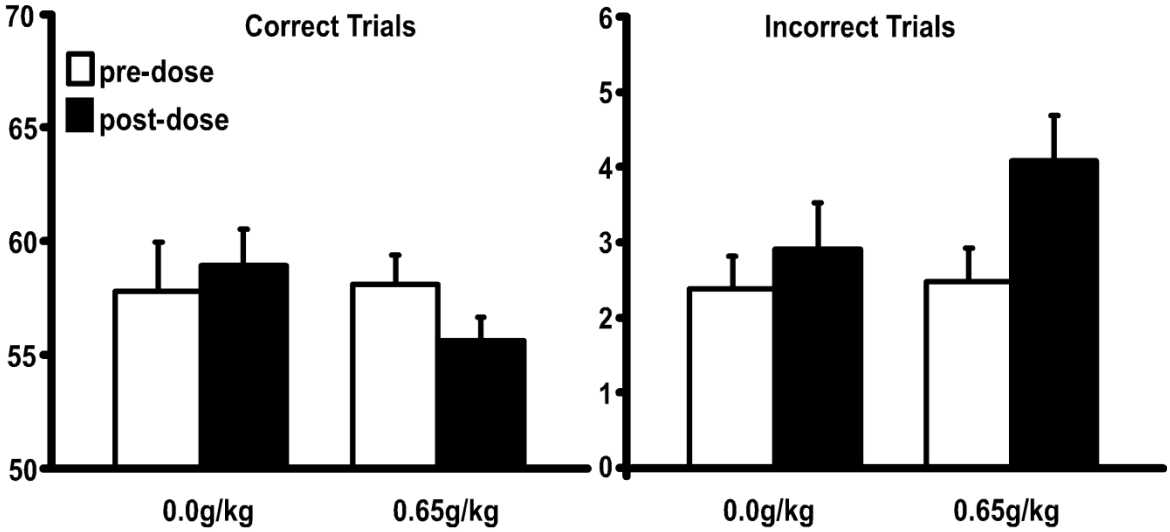

Figure 4.3: Effect of alcohol on DSST correct and incorrect trials.

Note: Error bars represent 1 SE.

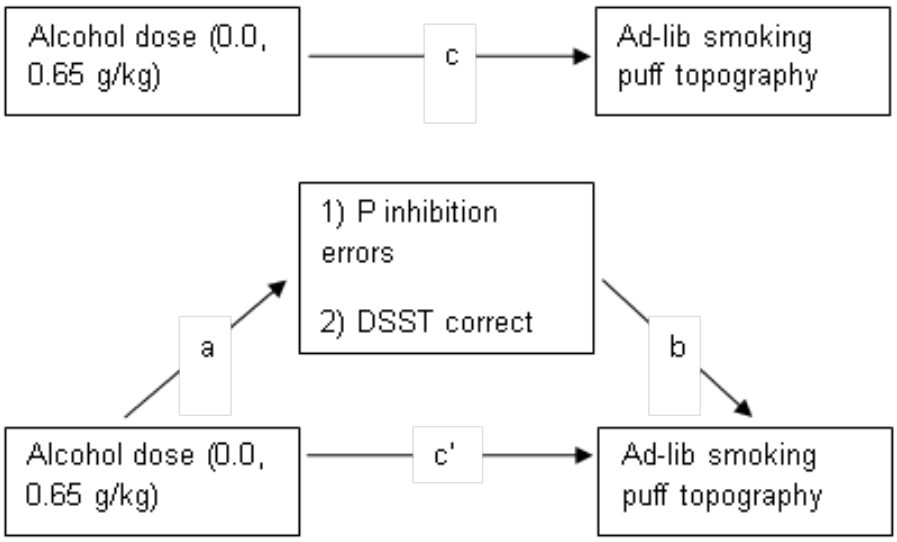

Figure 4.4: Path diagram for mediation analysis testing the direct and indirect effects of alcohol and proportion of inhibition errors (first model), and DSST correct trials (second model) on ad libitum smoking puff topography.

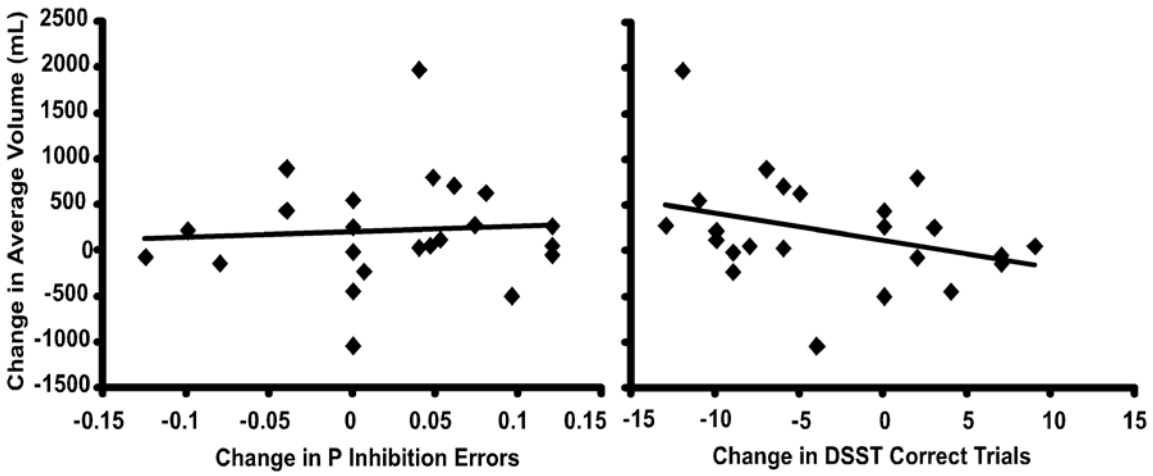

Figure 4.5: Scatter plots of the change in alcohol-induced p inhibition errors (left panel) and DSST correct trials (right panel) as a function of change in average volume per cigarette (mL).

Note: The change scores reflect an alteration in p inhibition errors, correct trials, and average volume between the alcohol and placebo post-dose assessments.

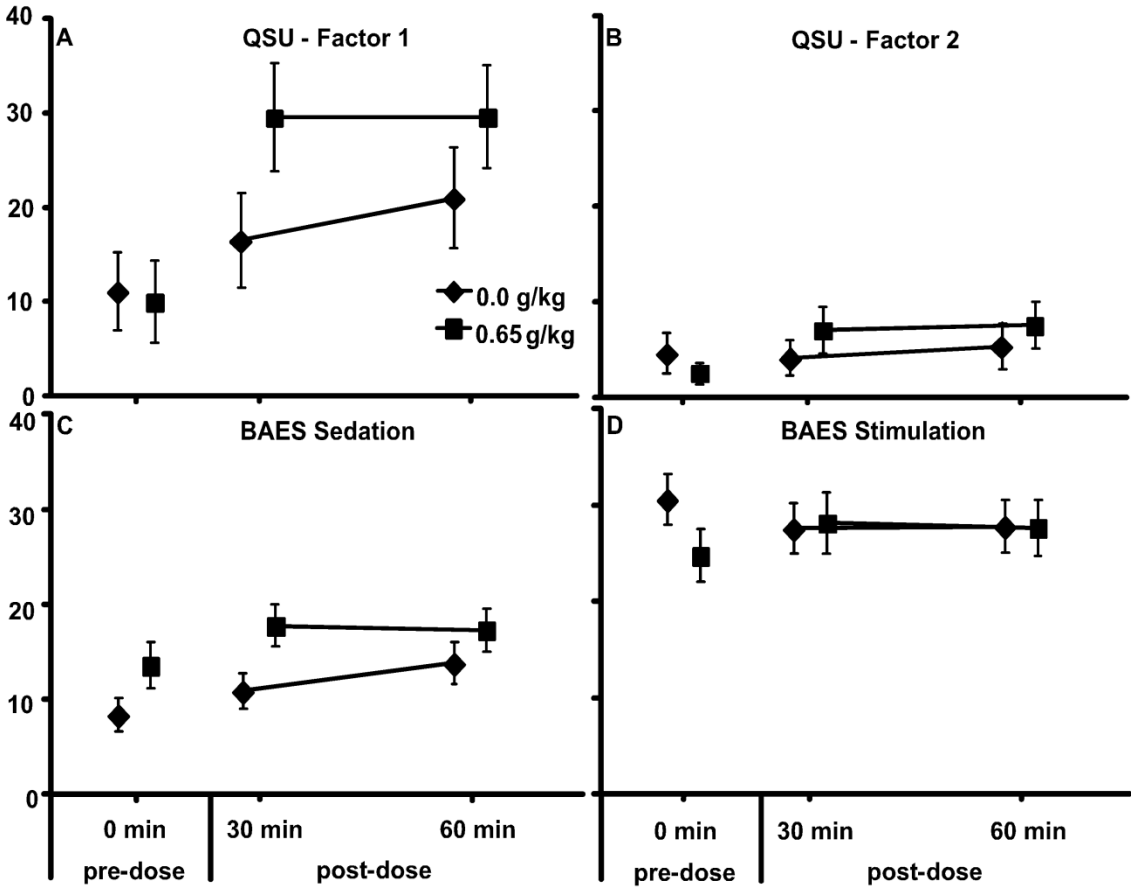

Figure 4.6: Effect of alcohol on QSU-B Factor 1 (Panel A) and Factor 2 (Panel B), and BAES Sedation (Panel C) and Stimulation (Panel D).

Note: Error bars represent ± 1 SE.

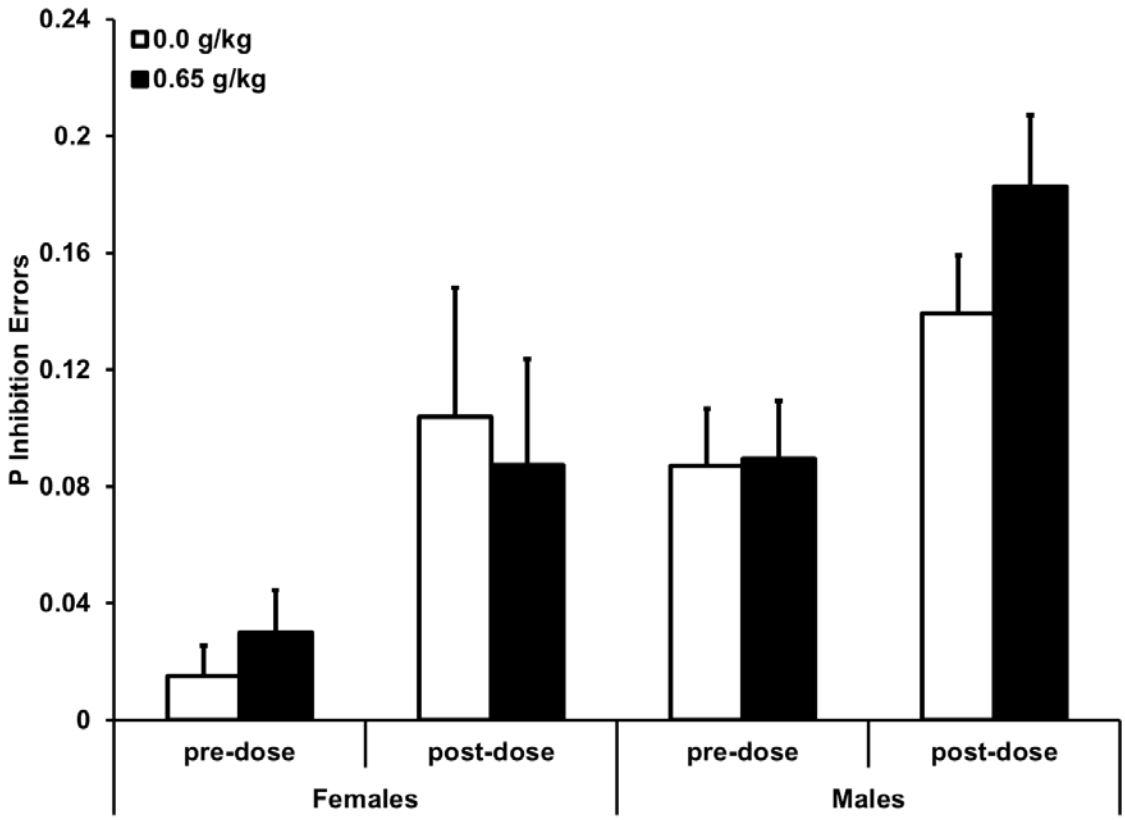

Figure 4.7: Effect of alcohol on proportion of inhibition errors to no-go targets following go cues as a function of gender and time (pre-dose to post dose).

Note: Placebo and alcohol administration were counterbalanced across subjects. Error bars represent 1 SE.

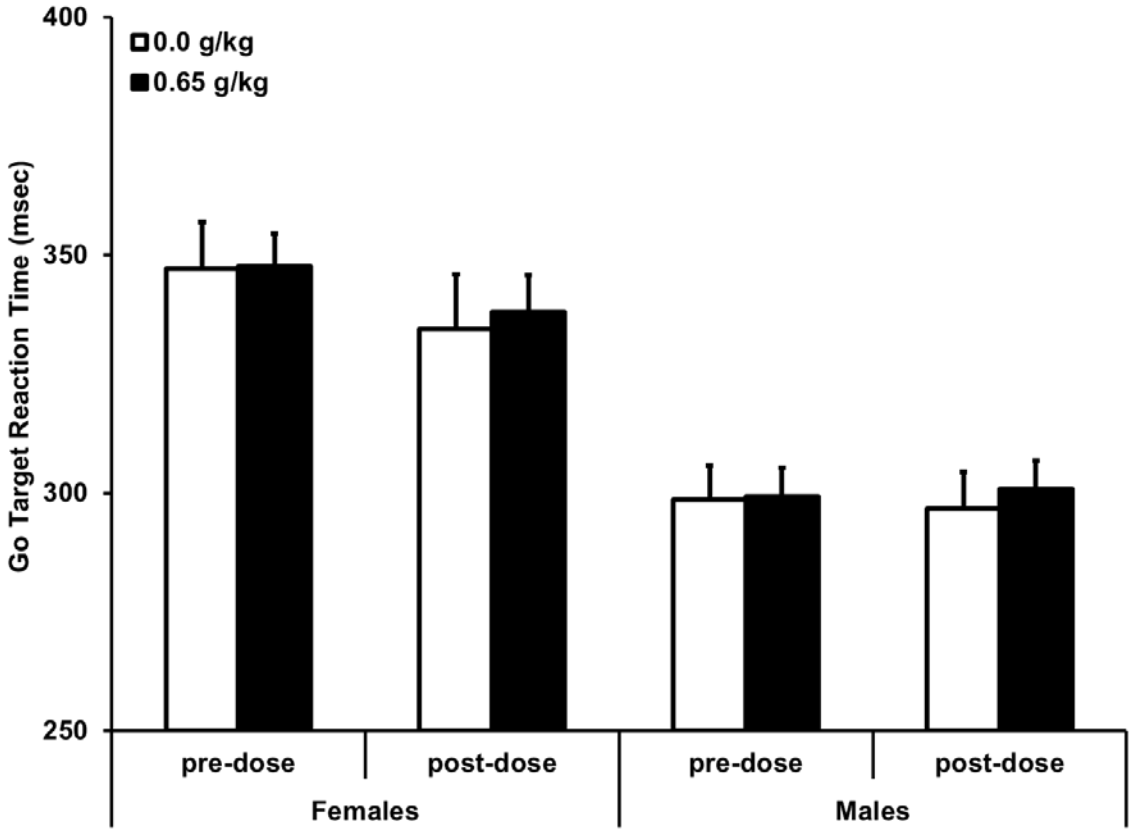

Figure 4.8: Effect of alcohol on reaction time to go targets following go cues as a function of gender and time (pre-dose to post dose).

Note: Placebo and alcohol administration were counterbalanced across subjects. Error bars represent 1 SE.

Chapter Five: General Discussion

The primary aims of the research in this dissertation were to determine the separate and combined effects of impulsivity and alcohol use on smoking escalation in young adults, and to determine if alcohol-impairment of inhibitory control mediated the relationship between acute alcohol administration and subsequent increases in cigarette smoking. Previous research has demonstrated that young adults (age 18-25) are at risk for escalation of tobacco use, and alcohol use has been consistently linked to concurrent and long-term increases in cigarette smoking. In addition, impulsivity is associated with initiation and escalation of alcohol and tobacco use, and acute alcohol impacts behavioral inhibition, suggesting that impulsivity can impact alcohol use, and alcohol use can alter impulsivity.

In a review on potential behavioral mechanisms underlying the relationship between smoking and drinking, Little (2000) suggested that there are two distinct components to the association between impulsivity, alcohol, and tobacco use: 1) dimensions of impulsivity can contribute to initiation of alcohol and tobacco use and the development of chronic use and dependence on each drug, and 2) the effects of the drugs themselves (specifically alcohol) can increase impulsive behavior, which could account for increases in cigarette smoking during drinking occasions. The work in this dissertation used a multi-modal approach to address both potential components described by Little (2000). First, correlational designs using both cross-sectional (Study 1) and longitudinal data (Study 2) were utilized to examine the independent influence of alcohol use

and dimensions of impulsivity as risk factors for initiation and escalation of smoking in young adults prior to entering college and during a three-year period following college enrollment. The advantage of this approach was that these relationships could be addressed using large sample sizes and longitudinal designs with repeated assessments of drug use and impulsivity across time. However, the limitations of the correlational approach precluded a direct examination of the causal relationship between alcohol and impulsivity on smoking behavior, which would address the second component identified in the Little (2000) review. In order to directly address this component, an experimental design was conducted to examine the effect of alcohol on inhibitory control and subsequent tobacco use in order to establish a potential causal link between alcohol-induced decrements in inhibitory control and subsequent increases in smoking (Study 3). Thus, utilizing both correlational and experimental designs provided a broad approach for addressing the relationship between alcohol use, impulsivity and smoking.

Alcohol Use and Smoking

Results from studies 1 and 2 demonstrated that alcohol use was associated with cigarette smoking. In Study 1, weekly alcohol use was associated with status as a non-daily and daily smoker, relative to non-smokers. However, alcohol use did not differentiate non-daily from daily smokers, suggesting that alcohol use was associated with tobacco use in general but did not differ based upon frequency of smoking. Study 2 expanded on the results of

Study 1 by examining initial alcohol use upon entry into college as a potential risk factor for subsequent escalation of smoking, and by determining if alcohol use changed as a function of smoking escalation. Results were similar to Study 1, with initial weekly alcohol use upon entry into college increasing the likelihood of belonging to a smoking group (i.e. high stable or decreasing smoking groups), indicating that initial weekly alcohol use was associated with status as a current smoker. Initial alcohol use did not increase the likelihood of belonging to the late-escalating smoking group, but weekly alcohol use did increase over the course of the three-year study in late escalators, indicating that escalation of both tobacco and alcohol use occurred in close proximity. Finally, Study 3 examined the acute effect of alcohol on ad-libitum smoking behavior in young adult occasional smokers and found that alcohol decreased latency to smoke and increased average puff volume and time per cigarette.

Taken together, these results provide further confirmation of the role of alcohol as a risk factor for acute and chronic increases in smoking and further support the wide-body of literature that has found a relationship between alcohol and tobacco use (e.g. Caldeira et al., 2012; Dierker et al., 2006; Harrison & McKee, 2008; Jackson et al., 2005, 2010; Krukowski et al., 2005; Reed et al., 2007, 2010; Shiffman & Paty, 2006; Weitzman & Chen, 2005; White et al., 2009; Witkiewitz et al., 2012). Given the clear findings in this dissertation and in the literature that alcohol use is risk factor for increasing both acute and long-term patterns of tobacco use in young adults, it is important to address alcohol use when targeting prevention and intervention strategies aimed at reducing tobacco

use in young adults. In addition, tobacco control policies banning smoking inside of establishments serving liquor are likely to further reduce concurrent alcohol and tobacco use.

Impulsivity and Smoking

This dissertation also provided evidence that dimensions of trait impulsivity were associated with frequency of tobacco use, and these associations occurred independently of alcohol consumption. Study 1 found that lack of premeditation was associated with non-daily smoking, and negative urgency was associated with daily smoking in individuals who reported smoking prior to entry in college. Study 2 found that sensation seeking increased the likelihood of belonging to the late-escalating smoking group relative to non-smokers, while negative urgency increased the likelihood of belonging to the high stable smoking group, relative to non-smokers and late-escalators. Study 2 was the first longitudinal study to find an association between UPPS dimensions of impulsivity and smoking group trajectories in young adults, and confirmed previous cross-sectional findings that sensation seeking is associated with initiation and current smoking status (Flory & Manuck, 2009; Lipkus et al., 1994; Perkins et al., 2000, Perkins et al., 2008; Spillane et al., 2010, 2012), and urgency is associated with heavier use and symptoms of dependence (Billieux et al., 2007; Doran et al., 2009; Spillane et al., 2010, 2012).

The finding that sensation seeking was associated with escalation of tobacco use in Study 2 is intriguing given that the overall goal of the dissertation

was to examine risk factors for escalation of tobacco use in young adults. This result is consistent with the wide-body of literature indicating that high sensation seekers are sensitive to the reinforcing effects of a variety of different drugs including alcohol (Fillmore et al., 2009; Magid & Colder, 2007), hallucinogens (Khavari, Mabry, & Humes, 1977), and stimulants (Bowling & Bardo, 1994; Kelly et al., 2006; Stoops et al., 2007). Tailoring prevention materials for high sensation seekers has been shown to increase intervention efficacy by reducing upward trends for marijuana use in adolescents (Palmgreen, Donohew, Lorch, Hoyle, & Stephenson, 2001), so this same strategy could be used to target young adult high sensation seekers who are vulnerable to increases in tobacco use.

It is important to acknowledge, however, that while sensation-seeking scores increased the likelihood of belonging to the late-escalating smoker group in Study 2, sensation seeking was not associated with status as a non-daily smoker in Study 1, a finding contrary to my hypothesis. Instead, the impulsivity dimension of lack of premeditation predicted non-daily smoking. Study 1 included college-bound individuals, so it is possible that legal or other social restrictions on smoking altered the typical relationship observed between sensation seeking and smoking, but this relationship then re-emerged in individuals that initiated smoking following entry into college in Study 2. However, more research is needed to further address this relationship.

Conversely, lack of premeditation was associated with non-daily smoking in Study 1, but did not uniquely predict smoking group membership in Study 2. It is important to note that in Study 1 the Wald-chi square estimate in the MLR

model for lack of premeditation was only trending toward significance, suggesting that the relationship between smoking and lack of premeditation was modest at best. Furthermore, in Study 2, lack of premeditation was associated with membership in the high stable group, but this relationship did not hold when alcohol was included in the model, suggesting the possibility that lack of premeditation might be more closely related to alcohol use than tobacco use. Alcohol use was most closely associated with non-daily smoking in Study 1 and high stable smoking in Study 2. Alternatively, it is possible that lack of premeditation might uniquely predict those who use alcohol and tobacco in combination (i.e. VanderVeen et al., 2013).

Negative urgency was a robust predictor of frequent smoking in each study, suggesting that behaving impulsively when upset may increase vulnerability to heavier patterns of tobacco use. Previous research has found that negative urgency is associated with greater negative affect craving responses to smoking cues (Doran et al., 2009), and heightened expectancies for the negative reinforcing effects of tobacco (Spillane et al., 2012), suggesting that those high in negative urgency may smoke more to relieve symptoms associated with negative affect. It is important to note that individuals who were high in negative urgency were already frequent smokers upon enrollment in studies 1 and 2, suggesting that negative urgency may be related to smoking uptake earlier in adolescence. One recent study found that negative urgency is associated with reports of smoking in the past six months in fifth grade students, demonstrating that negative urgency may predict vulnerability for smoking in

adolescents (Settles et al., 2012). More longitudinal research using a broader age range is needed to better understand the relationship between negative urgency and smoking uptake in adolescents and young adults. Nevertheless, the results of the current studies suggest that interventions targeting individuals who are high in negative urgency may be effective strategies for reducing escalation of tobacco use.

Mechanisms Underlying the Relationship between Alcohol and Tobacco Use

While alcohol was consistently associated with smoking frequency in the correlational studies, and acute alcohol increased smoking behavior in Study 3, alcohol impairment of inhibitory control did not mediate the direct effect of alcohol on ad-libitum smoking. This result was somewhat unexpected, given that previous research had found that individual differences in alcohol impairment of inhibitory control were associated with ad-libitum alcohol consumption (Weafer & Fillmore, 2008).

DSST performance is highly sensitive to the effects of alcohol and other drugs. While alcohol-induced changes in inhibition errors were unrelated to the association between alcohol and smoking, alcohol impairment of DSST performance did mediate the direct effect of alcohol on cigarette smoking, indicating that the study design was effective in engendering performance-based mediation of alcohol's effects on smoking. However, it is unclear whether this result provides insight into potential behavioral mechanisms underlying concurrent alcohol and tobacco use. Because DSST performance is highly

sensitive to alcohol and drug effects, it is possible that performance on this task serves as a nonspecific marker of sensitivity to alcohol effects and thus may serve as a marker of alcohol effects on other behavioral mechanisms not directly measured in this study.

Although it seems reasonable that the direct effect of alcohol on tobacco use may be driven by a pharmacological interaction between alcohol and nicotine, the primary psychoactive component of tobacco, multiple studies have failed to find that alcohol increases self-administration of nicotine (Perkins et al., 2005), and nicotine-containing cigarettes above denicotinized cigarettes (Barrett et al., 2013; King et al., 2009). However, it is possible that alcohol may increase the positive sensory experience and/or decrease the negative sensory effects of tobacco, independent of nicotine, which may be responsible for alcohol-related increases in tobacco use. Previous research has demonstrated that alcohol increases the positive sensory effects of tobacco, while reducing aversive effects associated with smoking (e.g. King et al., 2009; McKee et al., 2004; 2010). Individuals who report greater initial positive effects associated with smoking are more likely to become tobacco dependent (Ríos-Bedoya, Pomerleau, Neuman, & Pomerleau, 2009; Zabor et al., 2013), suggesting that alcohol's effects on the positive and aversive sensory experience of smoking could provide a rationale for the consistent relationship found between alcohol and tobacco use.

Conclusions and Future Directions

The series of studies in this dissertation provide evidence for the independent and combined effects of alcohol use and impulsivity as risk factors for escalation of tobacco use. However, future research is needed to address the limitations in the dissertation as well as replicating and extending the current findings in a wider population of young adults. First, future research should utilize more specific assessments of concurrent alcohol and tobacco use when evaluating risk factors associated with problematic use of both drugs. Recent studies have shown that individuals who report frequent concurrent use of alcohol and tobacco have greater levels of trait and behavioral impulsivity (Moallem & Ray, 2012; VanderVeen et al., 2013) than users of tobacco or alcohol alone. Since concurrent tobacco and alcohol users are vulnerable health-related effects and symptoms of abuse and dependence of both drugs, concurrent alcohol and tobacco users may be a target for tailored interventions to reduce the combined use of tobacco and alcohol.

Second, future research should address the relationship between alcohol, impulsivity, and tobacco use in populations that include individuals not attending college. While the results of the series of studies in this dissertation provides insight into the independent and combined effects of impulsivity and alcohol use as risk factors for escalation of tobacco use in young adults, the majority of the research was conducted using a population of college students. It will be important to determine whether these results will generalize to the broader population of young adults.

Finally, more laboratory research is needed to address potential mechanisms underlying concurrent alcohol and tobacco use. One possible approach is to examine non-nicotine pharmacological components or sensory effects of tobacco smoking that could be responsible for increasing the reinforcing effects of smoking following alcohol consumption. Research has identified non-nicotine pharmacological components of tobacco smoke (i.e. acetaldehyde and monoamine oxidase inhibitors) that may enhance the reinforcing effects of smoking alone or in combination with nicotine (for review see Rose, 2006). It is possible that the reinforcing properties in non-nicotine components of smoking may be further enhanced by alcohol, either alone or in combination with the increase in sensory effects of smoking (e.g. taste and olfactory cues, respiratory tract sensations), consistent with alcohol-induced increases in smoking of both placebo and active cigarettes that have been found in other studies (e.g. King et al., 2009; McKee et al., 2004; 2010). Finally, more laboratory research is needed to investigate alcohol-induced decrements in behavioral inhibition using a larger variety of measures, which would provide additional insight into whether other dimensions of behavioral inhibition may function as mechanisms for alcohol-induced increases in tobacco use.

In summary, this dissertation provides additional insight into the relationship between alcohol use, impulsivity and tobacco use in young adults. The studies provided further evidence that tobacco use is heterogeneous, and that young adults are at risk for escalation of tobacco use. In addition, the results of the studies showed a consistent relationship between alcohol use and

smoking, as well as providing evidence that trait measures of impulsivity are associated with smoking independent of alcohol use. These findings provide substantial evidence that alcohol use and trait impulsivity should be targeted in prevention and intervention strategies aimed at reducing tobacco use in young adults.

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Zuckerman, M. (1994). Behavioral expressions and biosocial bases of sensation seeking Cambridge university press.

Vita

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Education

2010 – Present – Ph.D. candidate, Behavioral Neuroscience and Psychopharmacology Program, Psychology, University of Kentucky, Lexington, KY

M.S. 2010 – Experimental Psychology, University of Kentucky, Lexington, KY; Thesis Title: Reward-Seeking Task Performance: A Validation Study

B.A. 2005 – Psychology and Philosophy, University of New Mexico, Albuquerque, NM: Magna Cum Laude with honors in Psychology Honors Thesis Title: No evidence for preferred rate of entrainment to synchronic stimuli in two performance-related tasks

Research Training

August 2007 – Present – Graduate Research Assistant, Residential Research Facility, Behavioral Neuroscience and Psychopharmacology Program, University of Kentucky, Lexington, KY Advisor: Thomas H. Kelly Ph.D.

August 2005 – July 2007 – Research Assistant, Nicotine Psychopharmacology Section, National Institute on Drug Abuse, Baltimore, MD Advisor: Stephen J. Heishman Ph.D.

August 2003 – May 2005 – Undergraduate Research Assistant, Functional Neuroimaging and Cognitive Neuroscience Lab, University of New Mexico, Albuquerque NM Advisor: Claudia D. Tesche Ph.D.

Teaching Opportunities

Spring 2011 – Laboratory Instructor, PSY 100 – Introduction to Psychology, University of Kentucky

Spring 2010 – Teaching Assistant/Guest Lecturer, PSY 312 – Brain and Behavior, University of Kentucky. Guest Lectures: Reproductive Behaviors, Biological Basis of Schizophrenia

Fall 2009 – Laboratory Instructor, PSY 216 – Application of Statistics in Psychology, University of Kentucky

Honors and Awards

Travel Award – UCLA Center for Advancing Longitudinal Drug Abuse Research Summer Institute (2012)

National Institute on Drug Abuse – Intramural Research Training Award (2005-7)

University of New Mexico - Magna Cum Laude in Psychology with Departmental Honors (2005)

Professional Affiliations

2005-7 Society for Research on Nicotine and Tobacco
2010-13 Society for Research on Nicotine and Tobacco
2007-13 College on Problems of Drug Dependence
2007-13 American Psychological Association, Student Affiliate, Division 28, Psychopharmacology and Substance Use

Service

March 2011 - SfN Brain Awareness Outreach presentation (Lafayette High School, Lexington Kentucky)

Journal Review (Ad hoc):

The American Journal on Addictions

Funding

F31 DA033728 (Lee DC) 4/1/12 – 3/31/14
NIH/National Institute on Drug Abuse
Individual Differences in Escalation of Tobacco Use: Impulsivity and Alcohol Use.
This grant is focused on examining dimensions of impulsivity and characteristics of alcohol use that may increase the vulnerability for acute and chronic escalation of tobacco use in young adults.
Sponsor: Thomas H. Kelly

Published Manuscripts

1. **Lee DC**, Perkins KA, Zimmerman E, Robbins G, Kelly TH (2011). Effects of 24-Hours of Tobacco Withdrawal and Subsequent Tobacco Smoking among Low and High Sensation Seekers. *Nicotine and Tobacco Research*, 13(10), 943-954.

2. Heishman SJ, **Lee DC**, Taylor, RC, & Singleton, EG (2010). Prolonged Duration of Craving, Mood, and Autonomic Responses Elicited by Cues and

Imagery in Smokers: Effects of Tobacco Deprivation and Sex. *Experimental and Clinical Psychopharmacology,* 18(3), 245-256.

3. **Lee DC**, Myers CS, Taylor RC, Moolchan ET, Berlin I, & Heishman SJ (2007). Consistency of Subjective Responses to Imagery-Induced Tobacco Craving Over Multiple Sessions. *Addictive Behaviors* 32, 2130-2139.

4. Martin T, Houck JM, Bish JP, Kicic D, Woodruff CC, Moses SN, **Lee DC** & Tesche CD (2006). MEG reveals different contributions of somatomotor cortex and cerebellum to simple reaction time after temporally structured cues. *Human Brain Mapping* 27, 552-561.

5. Martin T, Egly R, Houck JM, Bish JP, Barrera BD, **Lee DC** & Tesche CD (2005). Chronometric evidence for entrained attention. *Perception & Psychophysics* 67 (1), 168-184.

Manuscripts in Submission/Preparation

1. **Lee DC,** Peters JR, Adams ZW, Milich R, Kelly TH, & Lynam DR (submitted). Impulsivity and Alcohol Use are Associated with Cigarette Smoking in Young Adults

2. **Lee DC**, Charnigo RC, & Kelly TH (in revision). Individual Differences in Sensitivity to Monetary Reinforcement: A Comparison of Performance Tasks

3. **Lee DC,** Lile JA, Robbins CG, Matin CA, & Kelly TH (in preparation) Impulsivity and the Reinforcing, Subjective, and Cardiovascular Effects of Smoked Marijuana

Posters and Presentations

1. **Lee DC,** Martin CA, & Kelly TH (2013). Acute Effects of Alcohol on Inhibitory Control and Subsequent Tobacco Use in Young Adult Occasional Smokers. Poster: College on Problems of Drug Dependence.

2. Freeman MM*, **Lee DC,** Lile JA, Martin CA, & Kelly TH (2013). The Effect of Prior Month Marijuana Use on Marijuana Self-Administration in the Laboratory. Poster: University of Kentucky Center for Clinical and Translational Science Conference
*: Undergraduate Student Mentee

3. **Lee DC**, Adams ZW, Milich R, Kelly TH, & Lynam DR (2013). Analysis of the Relationship Between Impulsivity and Developmental Trajectories of Cigarette Smoking in a Longitudinal Study of Young Adults. Poster: Society for Research on Nicotine and Tobacco

4. **Lee DC**, & Kelly TH (2013). Acute Effect of Alcohol on Inhibitory Control and Subsequent Tobacco Use in Young Adult Occasional Smokers. Oral Presentation (Invited): Dartmouth University

5. Kelly TH, Lile JA, **Lee DC*,** Jiang Y, & Bardo MT (2012). A Translational Analysis of Impulsivity and Drug Abuse Vulnerability. Oral Presentation: Society for Neuroscience.
   *: Presenting author

6. **Lee DC** (2012). Longitudinal Study of the Association Between Impulsivity and Tobacco Use Among Young Adults. Oral Presentation (Invited): University of Kentucky Center for Clinical and Translational Science Seminar Series

7. **Lee DC,** Adams ZW, Milich R, Kelly TH, & Lynam DR (2012). Longitudinal Study Examining the Association Between Impulsivity and Developmental Trajectories of Cigarette Smoking in Young Adults. Poster: UCLA Center for Advancing Longitudinal Drug Abuse Research Summer Institute

8. Kelly TH, **Lee DC**, Robbins G, Martin CA, & Lile JA (2012). Impulsivity and d-Amphetamine Self-Administration. Oral Presentation: College on Problems of Drug Dependence

9. Martin CA, **Lee DC**, Lile JA, Robbins G, Guenthner G, & Kelly TH (2012). Marijuana use and its relationship to problematic drinking in young adult marijuana study volunteers. Poster: College on Problems of Drug Dependence

10. **Lee DC,** Adams ZW, Milich R, Kelly TH, & Lynam DR (2012) Longitudinal Study of the Association Between Impulsivity and Tobacco Use Among Young Adults. Poster: College on Problems of Drug Dependence

11. **Lee DC,** Adams ZW, Milich R, Kelly TH, & Lynam DR (2012) Behavioral and Trait Impulsivity Among Young Adult Intermittent and Daily Cigarette Smokers. Poster: Society for Research on Nicotine and Tobacco.

12. **Lee DC**, Lile JA, Robbins G, Martin CA, & Kelly TH (2011) Marijuana Self-Administration in High- and Low- Impulsive Sensation Seekers Using a Modified Progressive-Ratio Procedure. Poster: College on Problems of Drug Dependence.

13. **Lee DC**, Lile JA, Robbins G, Martin CA, & Kelly TH (2011) Marijuana Self-Administration in High- and Low- Impulsive Sensation Seekers Using a Modified Progressive-Ratio Procedure. Poster: Society for Prevention Research.

14. **Lee DC**, Lile JA, Robbins G, Martin CA, & Kelly TH (2010) Marijuana Self-Administration Under a Modified Progressive-Ratio Procedure in Humans: Effects of Marijuana Use History. Poster: College on Problems of Drug Dependence.

15. **Lee DC**, Robbins G, Perkins KA, & Kelly TH (2010) Effects of 24-Hours of Tobacco Withdrawal and Subsequent Tobacco Smoking in Male and Female Smokers. Poster: Society for Research on Nicotine and Tobacco.

16. **Lee DC**, Robbins G, & Kelly TH (2009) Reward-Seeking Task Performance: A Validation Study. Poster: College on Problems of Drug Dependence.

17. **Lee DC**, Robbins G, Martin CA, Lile, JA, & Kelly TH (2008) Methylphenidate Self-Administration in High- and Low-Impulsive Sensation Seekers Using a Progressive-Ratio Procedure. Poster: College on Problems of Drug Dependence.

18. **Lee DC**, Myers CS, Taylor RC, Moolchan ET, Berlin I, & Heishman SJ (2007) Consistency and Reliability of Responses to Imagery-Induced Tobacco Craving Over Multiple Sessions. Poster: Society for Research on Nicotine and Tobacco.

19. **Lee DC**, Myers CS, Taylor RC, Moolchan ET & Heishman SJ (2006) Working memory deficits during nicotine and tobacco withdrawal. Poster: Eastern Psychological Association.

20. Swartout JC*, **Lee DC**, Myers CS, Taylor RC, Moolchan ET & Heishman SJ (2006) EEG changes during nicotine and tobacco withdrawal. Poster: Eastern Psychological Association.
*: Undergraduate Student Mentee

21. **Lee DC**, Myers CS, Taylor RC, Moolchan ET, Berlin I & Heishman SJ (2006) Denicotinized cigarettes attenuate nicotine withdrawal symptoms and attentional deficits during an 8-day period. Poster: Society for Research on Nicotine and Tobacco.

22. **Lee DC**, Martin T, & Tesche CD (2004) Investigating symbolically cued temporal attention with MEG. Poster: Society for Neuroscience.