Individual Differences in Subjective Response to Alcohol:

Pharmacokinetic and Pharmacodynamic Factors

by

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A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved April 2014 by the
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ARIZONA STATE UNIVERSITY

August 2015

ABSTRACT

Variability in subjective response to alcohol has been shown to predict drinking behavior as well as the development of alcohol use disorders. The current study examined the extent to which individual differences in alcohol pharmacokinetics impact subjective response and drinking behavior during a single session alcohol administration paradigm. Participants ($N = 98$) completed measures of subjective response at two time points following alcohol consumption. Pharmacokinetic properties (rate of absorption and metabolism) were inferred using multiple BAC readings to calculate the area under the curve during the ascending limb for absorption and descending limb for metabolism. Following the completion of the subjective response measures, an ad-libitum taste rating task was implemented in which participants were permitted to consume additional alcoholic beverages. The amount consumed during the taste rating task served as the primary outcome variable. Results of the study indicated that participants who metabolized alcohol more quickly maintained a greater level of subjective stimulation as blood alcohol levels declined and reported greater reductions in subjective sedation. Although metabolism did not have a direct influence on within session alcohol consumption, a faster metabolism did relate to increased ad-libitum consumption indirectly through greater acute tolerance to sedative effects and greater maintenance of stimulant effects. Rate of absorption did not significantly predict subjective response or within session drinking. The results of the study add clarity to theories of subjective response to alcohol, and suggest that those at highest risk for alcohol problems experience a more rapid reduction in sedation following alcohol consumption while simultaneously experiencing heightened levels of stimulation. Variability in

pharmacokinetics, namely how quickly one metabolizes alcohol, may be an identifiable biomarker of subjective response and may be used to infer risk for alcohol problems.

DEDICATION

For my parents and grandparents who know the value of education.

ACKNOWLEDGMENTS

Data collection for the following study was a challenging endeavor that would have been impossible to do alone. I am grateful to Jonathan Gates, Nevena Ashminova, Ashley Akramoff, Alysia Spencer, Thai Ong, Andrew Doty, Anna Papova, Jessica Hartman, Rachel Grose, Sam Blankenship, and Jenna Leger, who devoted their time and efforts to make this study possible.

I would also like to acknowledge my graduate student colleagues, Caitlin Scott and Kyle Menary, who provided helpful feedback and encouragement during all phases of the study design and implementation. Caitlin and Kyle spent many late nights assisting with data collection, even though they were not required to do so. I am humbled by their support.

This dissertation has benefited greatly by the feedback from my dissertation committee: Drs. Laurie Chassin, Dave MacKinnon, and Foster Olive. Each provided tremendous insight and thoughtful, constructive suggestions that have greatly enhanced this document. I am fortunate to have access to committee members whose expertise aligns so well with this dissertation topic.

Finally, I would like to acknowledge the support of my dissertation chair and mentor, Dr. Will Corbin. Simply put, this dissertation would not exist without Will's help. His encouragement throughout this process has provided confidence in my ability to follow through with this and any future endeavors I will pursue. He devoted his time, financial resources, and expertise to ensure the completion of this study. Will has been a model mentor that I can only hope to emulate in my future career.

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INTRODUCTION

Alcohol is one of the most commonly used addictive substances in the world (Rehm et al., 2009). While most consumers of alcohol do so responsibly with little or no negative consequences, the prevalence of alcohol-related problems and disorders in the United States remains high. It is estimated that roughly a third of all fatal car accidents are linked to alcohol use (NHTSA, 2012), and alcohol is present in nearly 33% of injury-related emergency room visits (MacLeod & Hungerford, 2011). The prevalence of alcohol related problems is especially high among college students, in which heavy episodic, or binge, drinking is particularly prevalent (Knight et al., 2002). The problems associated with alcohol misuse on college campuses are abundant, and may include damage to self as well as institutional costs. The risks associated with alcohol use have been shown to follow a dose-response pattern, with the likelihood of injury increasing non-linearly with increased consumption (Taylor et al., 2010). Given the personal and societal burdens attributable to excessive alcohol use, considerable research has focused on identifying specific individual and environmental factors that may contribute to the development of alcohol problems and alcohol use disorders (AUD).

Although research on the familial transmission of alcohol use disorders has long established the heritability of problematic drinking (Liu et al., 2004; McGue, 1997; Prescott & Kendler, 1999), our understanding of the mechanisms through which genetics contribute to alcohol-related problems is quite limited. One potential mechanism of genetic influence is individual differences in subjective responses (SR) to alcohol. Research examining subjective evaluations of alcohol's intoxicating effects has suggested

that individual differences in response to alcohol may represent an endophenotype, or vulnerability marker, that is associated with a genetic risk for AUDs, though the pattern of response that confers greatest risk for alcohol related problems is unclear (Heath & Martin, 1991; Morean & Corbin, 2010; Quinn & Fromme, 2011; Ray, Mackillop, & Monti, 2010; Viken, Rose, Morzorati, Christian, & Li, 2003). While some researchers examining the influence of SR to alcohol have found that greater subjective stimulation and decreased impairment is related to increased levels of consumption, others have suggested that an attenuated response to the full range of pharmacological effects of alcohol is a more salient predictor of alcohol problems (Morean & Corbin, 2010; Newlin & Thomson, 1990; Schuckit, 2004). If SR is to become a reliable indicator of alcohol risk, then the specific patterns of response to alcohol associated with alcohol problems must be clearly delineated, as well as the factors that contribute to these response types.

Response to alcohol is comprised of two parallel aspects of alcohol pharmacology: pharmacokinetics and pharmacodynamics. Pharmacokinetic processes represent the ways in which the body manipulates the drug after consumption and includes the absorption, distribution, metabolism, and excretion of the drug (Ramchandani, Bosron, & Li, 2001). Pharmacodynamics represent the processes by which the drug manipulates the body after consumption (Lees, Landoni, Giraudel, & Toutain, 2004; Ray et al., 2010). While the intensity and duration of alcohol's effects are driven by the pharmacokinetic aspects of alcohol (i.e., absorption, distribution, and metabolism), the behavioral and subjective effects of alcohol arise from an array of pharmacodynamic factors (i.e., how the drug affects the body) (Ray et al., 2010). Subjective response represents an interpretation of the pharmacodynamic properties of

alcohol; however, the intensity and duration of the effects experienced is largely determined by factors (e.g. dose, timing) that contribute to variations in alcohol pharmacokinetics. First and foremost, the typical pharmacodynamic processes experienced as a result of alcohol consumption vary as a function of the concentration of alcohol in the bloodstream. Low to moderate doses of alcohol (e.g., .02 - .08 % BAC) typically result in subjective feelings of relaxation and euphoria. At higher levels of alcohol intoxication (e.g., .10 - .29 % BAC) emotional lability is more common (Dubowski, 2006). Environmental factors, including diet and rate of consumption, have also been found to influence the pharmacokinetics of alcohol, which in turn modulates SR to alcohol effects (Holt, 1981). Individual differences in alcohol pharmacokinetics that are unrelated to environmental or contextual factors, may also contribute to SR; however, few studies have examined this hypothesis. If SR to alcohol represents an endophenotype of risk for alcohol problems, then individual variability in the factors that contribute to the pattern of SR should also be evident. In summary, factors known to influence pharmacokinetics appear to play an instrumental role in the type and extent of SR experienced; however, the nature of the relations between these two processes, as well their combined influence on subsequent drinking behavior, remains to be elucidated.

Evidence from alcohol administration studies has demonstrated considerable individual variability in subjective experience of the pharmacological effects of alcohol. Some individuals report greater sensitivity to the stimulant effects of alcohol, which are generally viewed as enjoyable and positively reinforcing (Earleywine & Martin, 1993; Erblich, Earleywine, Erblich, & Bovbjerg, 2003). Others endorse greater sensitivity to the more aversive sedative effects (Earleywine and Martin, 1993; Erblich et al., 2003).

While individuals differ in how they subjectively experience the effects of alcohol, there is also considerable variability in alcohol pharmacokinetics, as a result of both genetic and environmental factors (Norberg, Jones, Hahn, & Gabrielsson, 2003; Ramchandani et al., 2001). These variations in alcohol pharmacokinetics likely play a role in the type and extent of SR experienced. To our knowledge, no studies have directly examined relations between the pharmacokinetics and pharmacodynamics of alcohol and how these parallel processes relate to drinking behavior.

ALCOHOL PHARMACOKINETICS

Pharmacokinetics represents the branch of pharmacology that is focused on understanding the physiological processes that occur within an organism in response to an ingested substance, and the changes that occur to the substance as a result of these processes (Lees et al., 2004). The pharmacokinetic properties of alcohol have been examined extensively over the past 80 years, and are well documented. After alcohol is consumed, it is almost completely absorbed, primarily through the duodenum of the small intestine by passive diffusion (Norberg et al., 2003). Absorption begins as soon as the drug enters the stomach, and the emptying of the stomach contents into the small intestine determines the rate at which alcohol enters the bloodstream. Once in the bloodstream, alcohol is distributed throughout the body, and is largely governed by the total body water present in the various organs and tissues (Ramchandani et al., 2001). The elimination of alcohol from the body occurs primarily as a result of metabolism, with small amounts of the drug being excreted in the breath (0.7%), urine (0.3%) and sweat (0.1%) (Holford, 1987). Almost all of ingested alcohol is metabolized in the liver (92-95%) by a two-step hepatic process. Alcohol is converted into acetaldehyde by the

enzyme alcohol dehydrogenase (ADH), and is further broken down into acetate by aldehyde dehydrogenase (ALDH) (Kalant, 1996).

The kinetics of alcohol are commonly modeled using a formula proposed by Widmark (1932), in which ethanol is distributed almost instantaneously at the rate of absorption and exits the body at a constant rate independent of the concentration of alcohol (Kalant, 1996). The model is best displayed in terms of blood alcohol concentrations (BAC), in which BAC rises sharply following consumption before peaking and eliminating at a constant rate. The model proposes that the kinetics of alcohol are generally consistent, with little variability across individuals. Numerous studies have documented the virtually linear descent of BAC over time (Kalant, 1996). Others have noted, however, that the metabolism of alcohol follows Michaelis-Menten kinetics, such that the rate of elimination of alcohol from the body depends on the amount of alcohol consumed (Norberg et al., 2003). In general, though, the shape of the BAC curve is generally established for a given dose of alcohol, and can be broken down into four components that are illustrated in Figure 1. Upon consumption of alcohol, BAC levels quickly rise, demonstrating the rapid rate of absorption (step 1). As the BAC approaches peak level there is a brief plateau (step 2), before a rapid drop until rate of metabolism reaches equilibrium (step 3). Following this equilibrium, BAC levels decline at a steady rate that is nearly linear (Dubowski, 1985). These known attributes of the kinetics of alcohol are often utilized in forensic settings to establish approximate BAC at the time of arrest when motorists are cited for driving under the influence of alcohol (Dubowski, 1985). Others, however, have noted considerable variability in the

pharmacokinetics of alcohol, which challenges the utility of blood alcohol concentrations in forensic settings.

VARIABILITY IN ALCOHOL PHARMACOKINETICS

While the kinetics of alcohol are generally understood, several factors, both genetic and environmental, contribute to variability across all aspects of alcohol pharmacokinetics (Norberg, Gabrielsson, Jones, & Hahn, 2000; Norberg, Jones, Hahn, & Gabrielsson, 2003). The rate at which alcohol is absorbed, distributed, and metabolized varies by as much as three to four times between individuals (Friel, Baer, & Logan, 1995; Ramchandani et al., 2001). Given the relations between the pharmacokinetic and pharmacodynamic processes noted previously, it is likely that individual differences in pharmacokinetic processes would result in corresponding variability in subjective response to alcohol.

The greatest variability in the pharmacokinetics of alcohol occurs during absorption (Friel et al., 1995; Norberg et al., 2003; Ramchandani et al., 2001). Wide inter- and intra-individual variation has been demonstrated in both the rate of absorption and peak BAC, which is influenced largely by the rate of gastric emptying (Kalant, 1996; Norberg et al., 2003). Several environmental factors have been shown to modulate gastric emptying; delaying the rate of absorption. The primary factor regulating the rate of absorption is whether alcohol is consumed on an empty or full stomach (Kalant, 1996). When alcohol is consumed in a fasted state, the rate of gastric emptying from the stomach to the small intestine is increased, relative to consumption following a meal (Fraser & Rosalki, 1995; Norberg et al., 2003). Identical weight adjusted doses of ethanol administered in a fasted state result in peak BAC that are significantly higher and occur

more quickly than when consumed following a meal (Fraser & Rosalki, 1995). Other factors known to influence gastric emptying, including cigarettes and certain medications, such as aspirin, have been found to reduce the rate of absorption of ethanol (Johnson, Horowitz, Maddox, Wishart, & Shearman, 1991; Kechagias, Jönsson, Norlander, Carlsson, & Jones, 1997).

Rate of absorption is also influenced by drinking characteristics, including the type and dose of alcohol consumed, and the rate of consumption (Fillmore & Vogel-Sprott, 1998; Norberg et al., 2003; Roine et al., 1993). Smaller doses of alcohol result in faster absorption, as does increasing the rate of consumption (Roine et al., 1993). Studies have shown that faster drinking also results in greater impairment in psychomotor functioning (Jones & Vega, 1973; Moskowitz & Burns, 1976). Although many factors contribute to the wide variability found in the absorption of alcohol, it is clear that faster absorption is related to greater intoxicating effects (Holt, 1981). When alcohol is absorbed more rapidly, the peak concentration is higher and subjective intoxication greater (Holt, 1981; Norberg et al., 2003).

The metabolism and elimination of ethanol is less variable between individuals than absorption, and has a stronger genetic component (Friel et al., 1995; Ramchandani et al., 2001). The enzymes primarily responsible for the metabolism of ethanol, ADH and ALDH, are localized primarily in the liver (Norberg et al., 2003). The rate of elimination of alcohol from the blood varies both between and within individuals based on genetic and environmental factors that influence these ethanol metabolizing enzymes. The genes responsible for ADH and ALDH play a role in determining the rate at which alcohol is metabolized, which influences the nature and intensity of the subjective response (Ray et

al. 2010). The genes responsible for the various forms of ADH are linked to chromosome 4, and variations in these genes have a substantial effect on the rate at which alcohol is metabolized into acetaldehyde (Ramchandani et al., 2001; Ray et al., 2010). The speed of metabolism is eight times faster for an individual with the ADH1B-2 and ADH1C-1 alleles than an individual with the ADH1B-1 and ADH1C-2 alleles (Lee, Chau, Yao, Wu, & Yin, 2006). Faster metabolic activity of ADH increases the presence of acetaldehyde, which results in aversive effects, including flushing, headache, and nausea (Ray et al., 2010). Greater accumulation of acetaldehyde is also influenced by genetic variants in ALDH. Individuals with the ALDH2-2 allele, which is commonly found in individuals of East Asian ancestry, are less able to metabolize acetaldehyde to acetate (Luczak, Glatt, & Wall, 2006; Whitfield, 2002). Disulfiram, a medication used in the treatment of alcohol dependence, operates through the same pharmacokinetic pathway associated with the ALDH2-2 allele and results in an increase of acetaldehyde by blocking ALDH (Ray et al., 2010).

Environmental factors have also been shown to influence the metabolic processing of alcohol. While food intake has a marked effect on the absorption of alcohol due to its relation to gastric emptying, the fed or fasting state of the individual also has an effect on metabolism. When alcohol is consumed with food the rate of metabolism and elimination is slower (Kalant, 1996). The most convincing evidence for the role of food on metabolism is found in studies utilizing intravenous administration of ethanol in which the absorption of ethanol through the gastrointestinal tract is bypassed. When alcohol is administered intravenously following a high carbohydrate meal, the rate of metabolism is increased (Ramchandani et al., 2001). Other factors, including physical

exercise and concurrent use of medications and other drugs also influence the metabolism of ethanol (Kalant, 1996; Norberg et al., 2003; Ramchandani et al., 2001).

Despite the inter- and intra-subject variability inherent in the pharmacokinetics of alcohol, most studies involving alcohol administration with human samples have attempted to reduce individual differences in alcohol pharmacokinetics, and given little attention to remaining variability. While standard alcohol administration protocols involve efforts to control variability in BACs (i.e., administering weight adjusted doses and limiting food consumption prior to alcohol consumption), few studies assess for within and between subject variability in BAC. Evidence from our own lab-based alcohol administration studies suggests that individual variability in BAC curves is considerable, even after controlling for factors known to affect pharmacokinetics (e.g., time since last meal; quantity, type, and duration of drinking). Figure 2 displays BAC curves for five participants from a recent study in our lab who achieved similar peak BACs. Variability is clearly evident in the slope of the descending limb of the curve, as well as the amount of time that peak BAC is maintained. Variability in the rate of ascent on the ascending limb is less apparent, and is likely attributable to the rapid rate of change in BAC associated with the dosing protocol and infrequent measurements of BAC in this study. The current study will use a more rapid dosing procedure following a light snack, and will measure participant BACs at regular ten minute intervals, thereby providing more precise representations of changes in BAC over time.

SUBJECTIVE RESPONSE TO ALCOHOL

Considerable variability in subjective response to alcohol exists, and the degree and type of subjective response to alcohol experienced have been shown to predict within

session drinking behavior, and the predisposition for alcohol abuse and dependence (Corbin, Gearhardt, & Fromme, 2008; King et al., 2002; King, de Wit, McNamara, & Cao, 2011; Morean & Corbin, 2008; Schuckit & Smith, 2000; Schuckit & Tipp, 1997). Numerous alcohol challenge studies have been conducted to assess SR following alcohol consumption and its relation to within and between session drinking as well as risk for alcohol use disorders. Two theories have been indicated as potential explanatory models of the relationship between subjective response to alcohol and pathological drinking. The Low Level of Response (LLR) Model suggests that individuals differ in their sensitivity to the wide range of pharmacological effects that are associated with alcohol. The model has been developed and tested over the past several decades by Schuckit and colleagues (1999), and suggests that those with a propensity for heavy alcohol use have an attenuated response to the effects of alcohol. A competing model, the Differentiator Model, stipulates that, rather than a global reduction in sensitivity to alcohol effects, those at high risk for AUDs experience an increase in sensitivity to the positive effects of alcohol, and a decreased sensitivity to negative effects compared to those at lower risk for the disorder (Morean & Corbin, 2010; Newlin & Thomson, 1990).

The LLR model was first proposed thirty years ago by Schuckit (1984) after finding that sons of alcoholic fathers experienced reduced subjective response to alcohol, compared to participants without a family history of alcoholism. Subsequent studies by Schuckit and colleagues replicated these earlier findings, and further suggested that individuals who experience an attenuated response to alcohol are more likely to develop alcohol dependence (Schuckit, 2004). In a sample of 315 sons of alcoholic fathers, Schuckit and colleagues (2004) found that a LLR predicted the development of AUD 20

years later, over and above the effect of family history. The authors suggest that subjective response to alcohol is a preexisting characteristic that affects how the individual interprets experiences related to alcohol use. An initial LLR may contribute to greater alcohol consumption, as the individual must drink more to achieve the desired positive effects from alcohol use that others receive at lower doses (Schuckit et al., 2004). In this way LLR may be related to the acquisition of tolerance. Although the LLR model has received considerable support, several studies have failed to replicate the finding that a LLR to alcohol is associated with increased consumption and greater likelihood of alcohol dependence (Conrod, Peterson, Pihl, & Mankowski, 1997; Morzorati, Ramchandani, Flury, Li, & Connor, 2002).

The LLR model is based on the assumption that individuals at high risk for experiencing alcohol problems and developing AUDs are relatively insensitive to both the positive and negative effects of alcohol. While experiencing fewer negative effects from alcohol use may lead to increased consumption, the assumption that a decrease in positive effects of alcohol should lead to greater consumption seems intrinsically flawed (Morean & Corbin, 2010). Individuals who receive less positive reinforcement from alcohol should have less, not more, motivation to drink. An alternative model, the Differentiator Model, suggests that individuals at risk for developing AUDs have an increased sensitivity to the rewarding effects associated with alcohol use and a decreased sensitivity to the negative effects of alcohol. According to this model, the subjective response to alcohol among high risk individuals reinforces the continued use of alcohol by enhancing the desirable pharmacological effects of alcohol while limiting aversive effects (Newlin & Thomson, 1990). While fewer studies have investigated the

Differentiator Model, support for the model has been indicated in heavy drinking samples. In a study comparing response to alcohol in heavy and light drinkers, King et al. (2002) found that, compared to lighter drinkers, participants classified as heavy drinkers reported heightened sensitivity to the positive stimulant effects of alcohol. This effect was most pronounced during the ascending limb of the BAC. Heavy drinkers also experienced significantly less sedation on the descending limb of the BAC. A recent meta-analytic review of the SR literature has provided further support for the Differentiator Model in predicting typical alcohol consumption (Quinn & Fromme, 2011). Heavier drinking men and women report significantly less sedation than lighter drinkers during the descending limb. On the ascending limb, endorsement of stimulation is half a standard deviation greater for heavier drinkers than lighter drinkers (Quinn & Fromme, 2011).

Although the LLR and Differentiator models offer unique perspectives as to how pharmacological responses to alcohol are perceived in problem and non-problem drinkers, neither model has been consistently supported (Morean & Corbin, 2010). One possible explanation for this discrepancy may be the time at which subjective alcohol effects were assessed during the drinking period. Research has suggested that the pharmacological effects of alcohol are biphasic in nature, that is, certain types of alcohol responses are more pronounced during the ascending limb of the blood alcohol curve, while other effects are more pronounced as blood alcohol levels decline (Earlywine & Martin, 1993; Erblich et al., 2003, Ray et al., 2010). Regarding SR to alcohol, it has been documented that as blood alcohol levels rise alcohol produces robust stimulating effects, and other effects that are generally rated positively (Earleywine and Martin, 1993;

Erblich et al., 2003). As blood alcohol levels decline, sedative effects predominate, as well as other effects that are typically viewed as undesirable (Earleywine and Martin, 1993; Erblich et al., 2003). Despite evidence that the pharmacological effects of alcohol vary by limb of the BAC, most alcohol administration studies investigating subjective response to alcohol have failed to consider the limb of the BAC curve (Morean & Corbin, 2010; Ray et al., 2010), and the measures used to assess SR have often failed to adequately capture both the positive and negative effects experienced following alcohol consumption (Morean & Corbin, 2010).

The primary measure of SR utilized in studies supporting the LLR model is the Subjective High Assessment Scale (SHAS). The SHAS has typically been utilized as a unidimensional construct of subjective intoxication. Principal components analysis of the original 38 items on the SHAS revealed a multiple factor solution in which 46% of the total variance was accounted by the first factor, which was labeled "maximum terrible feelings" (Schuckit, 1985). Results of these analyses suggest that the SHAS is most sensitive to the unpleasant effects of alcohol. As noted previously, response to alcohol has demonstrated biphasic attributes, with positive stimulant effects predominating the ascending limb of the BAC curve, and negative sedative effects more pronounced as BAC levels decline. While the SHAS may provide utility in assessing negative alcohol effects, the ability of the measure to properly capture positive, stimulant response to alcohol is questionable.

Although alcohol is classified as a sedative drug, it also produces considerable stimulant effects. The nature of the effects experienced following consumption of alcohol influence the drinking behavior of the individual. In order to fully understand the

relations between SR and subsequent drinking, measures of SR that assess both stimulant and sedative effects of alcohol intoxication must be used. The Biphasic Effects of Alcohol Scale was developed to capture both stimulant and sedative effects due to alcohol (Martin, Earleywine, Musty, Perrine, & Swift, 1993). Factor analysis of the 14 item scale confirmed the two factor structure. Consistent with the biphasic nature of alcohol effects, stimulant ratings were higher than sedative ratings on the ascending limb of the BAC curve, and lower than sedative ratings on the descending limb (Martin et al., 1993). Correlational analyses comparing the BAES and SHAS measures indicated that the SHAS is most strongly correlated with the sedation measure of the BAES (Ray et al., 2010). The stimulation subscale of the BAES has been found to be the strongest predictor of urge to drink, when both the BAES and SHAS were included in analyses (Ray et al., 2010). When both stimulation and sedation are assessed, greater alcohol-induced stimulation is also associated with increased within session consumption (Corbin et al., 2008).

When taken as a whole, the extant literature seems to provide more support for the Differentiator Model. While support for the LLR model has been found in heavy drinking populations, studies that have examined this effect have relied on measures that mainly assess effects consistent with the descending limb of the BAC. Accordingly, the low level of response experienced by heavy drinkers and individuals with AUD may be limited to effects on the descending limb of the BAC, which is consistent with the Differentiator Model (Morean & Corbin, 2010). Studies that have examined SR using measures that assess both stimulant and sedative effects (typically the BAES; Martin et al., 1993) have generally supported the Differentiator Model. Increased stimulant

response, as measured by the BAES, has been found to predict greater ad-libitum alcohol consumption (Corbin et al., 2008), and heavy drinkers report more stimulation following alcohol consumption than do light drinkers (King et al., 2002).

RELATIONS BETWEEN PHARMACOKINETICS AND SUBJECTIVE RESPONSE TO ALCOHOL

It is generally accepted that the faster drugs of abuse enter the brain the greater their potential for abuse (Samaha & Robinson, 2005; de Wit, Bodker, & Ambre, 1992). Drugs that are administered via routes that lead to faster absorption and distribution to the brain are associated with higher abuse liability (Samaha & Robinson, 2005). For example, inhaled cocaine ("crack") is believed to be more addictive than cocaine administered intranasally (de Wit et al., 1992; Hatsukami & Fischman, 1996). Smoked cigarettes provide a rapid distribution of nicotine to the brain, which may explain why cigarettes are particularly addictive compared to other products that deliver nicotine more slowly (e.g., moist snuff, nicotine replacement therapy) (Henningfield & Keenan, 1993; Samaha & Robinson, 2005). One possible explanation as to why more rapidly administered drugs promote addiction is because it leads to greater feelings of euphoria. Individuals endorse higher ratings of euphoria when cocaine is administered intravenously than intranasally (Abreu, Bigelow, Fleisher, & Walsh, 2001). Similarly, intravenous administration of heroin is associated with greater subjective ratings of pleasure and drug-liking than intranasal heroin administration (Comer, Collins, MacArthur, & Fischman, 1999). Although alcohol may be delivered through many routes of administration, including intravenous and percutaneous (through the skin), it is almost exclusively delivered via oral consumption (Kalant, 1996). Even so, greater

subjective intoxication and impairment is evident when alcohol is absorbed more rapidly (Holt, 1981).

The psychomotor stimulant theory of addiction postulates that all drugs of abuse activate stimulatory responses which positively reinforce continued use (Wise & Bozarth, 1987). Although alcohol is classified as a sedative drug, it also exhibits stimulation, as noted previously. Heavier drinkers and those at greater risk for alcohol use disorders experience greater feelings of intoxication following alcohol consumption. When rate of absorption is manipulated in alcohol administration studies, faster absorption rates lead to a greater sense of intoxication. Subjective feelings of intoxication represent an interpretation of a myriad of alcohol effects, both stimulant and sedative. While evidence demonstrating relations between pharmacokinetics and intoxication provides support for the influence of pharmacokinetic processes on subjective response to alcohol, the differences in pharmacokinetics in these studies are primarily due to environmental factors. Little is known about the extent of individual differences in alcohol pharmacokinetics and the relation of these differences to SR. Furthermore, studies that have examined relations between pharmacokinetics and SR have focused almost exclusively on subjective intoxication. Thus, the association between pharmacokinetics and the full range of alcohol effects is largely unknown. Variability in the absorption and metabolism of alcohol may relate to widely different experiences in stimulation and sedation. Faster absorption of alcohol, for example, may provide enhanced stimulation, which is positively reinforcing; thus increasing the desire for more alcohol and increasing the likelihood of further consumption. Slower metabolism of alcohol, on the other hand,

may lead to an increase in the aversive, sedative effects of alcohol and decrease the likelihood of continued use.

Newlin and Thomson's (1990) differentiator model of SR suggests that those at risk for alcohol problems may be more sensitive to the rewarding stimulant effects of alcohol and less sensitive to the unpleasant sedative effects. The authors further note the role of differences in pharmacokinetics and neurobiological mechanisms that may influence variation in SR. While it is clear that SR to alcohol is influenced by pharmacokinetic properties, the full extent of this influence in unknown. Faster absorption has been shown to increase the distribution of alcohol, which is associated with greater subjective intoxication. Less is known about the role of rate of absorption on other alcohol effects, including sedation. Variability has also been indicated in the metabolism and elimination of alcohol, but the relation of these kinetic properties to experienced subjective effects is unknown. Individuals with genetic polymorphisms that limit the metabolism of ethanol have been shown to experience greater aversive effects due to alcohol on the descending limb of the BAC curve, suggesting that a faster rate of metabolism is associated with increased risk for problematic drinking (Chen et al., 1999).

STUDY AIMS

The overarching aim of the current study was to examine relations between the pharmacokinetic and pharmacodynamic properties of alcohol, and how individual differences in these processes relate to within session drinking behavior. In doing so, we hoped to add clarity to the subjective response literature by identifying the patterns of subjective response that are associated with problematic drinking. The pharmacokinetic properties of alcohol were inferred by the rate of change in blood alcohol concentrations

(measured by area under the blood alcohol concentration curve) during both the ascending and descending limb, when measures of SR were assessed. Subjective response to alcohol served as an indicator of individual variability in alcohol pharmacodynamics. The first aim was to directly assess relations between rate of change in blood alcohol concentrations and SR to alcohol on both the ascending and descending limbs of the blood alcohol curve. Next, we aimed to examine the separate main effects of alcohol pharmacokinetic and pharmacodynamic properties on within session drinking outcomes, including craving and ad-lib consumption. Finally, the study aimed to assess the potential mediating influence of SR on the relation between the pharmacokinetic rate of change on the BAC curve and within session drinking behavior.

We first examined relations between the pharmacokinetic (i.e., changes in BAC curves) and pharmacodynamic (i.e., subjective response) properties of alcohol on both the ascending and descending limb of the BAC curve. Identical measures of SR were assessed at corresponding BAC levels on the ascending and descending limb. Using BAC curves plotted for each participant, we assessed the rate of change in BAC for each participant on both the ascending and descending limb. Rate of change was determined for each participant by calculating the area under the blood alcohol concentration curve (AUC) for both the ascending and descending limb. It was hypothesized that a smaller AUC on the ascending limb, indicating more rapid absorption, would be associated with greater stimulation. Greater AUC on the descending limb, indicating slower metabolism and elimination of alcohol was expected to be associated with more sedation. Subjective sedation is less pronounced on the ascending limb of the BAC curve, and subjective stimulation is less pronounced on the descending limb, and few studies have examined

these aspects of SR. Thus, although the analytic models include paths from the BAC parameters to ascending limb sedation and descending limb sedation, these analyses were exploratory in nature.

It was further hypothesized that differences in pharmacokinetic and pharmacodynamic processes would uniquely predict drinking behavior. It was expected that greater subjective stimulation on the ascending limb and less subjective sedation on the descending limb would predict increased craving and greater beer consumption during a taste rating task. As noted previously, ascending limb sedation and descending limb stimulation have received little attention in the literature. Thus, analyses involving relations among these SR measures, craving and ad-lib consumption were exploratory in nature.

Regarding pharmacokinetic processes, it was expected that a more rapid rate of change in BAC on the ascending limb would result in greater self-reported craving and greater ad-lib consumption. On the descending limb, it was expected that a more rapid decline in BAC would predict increased craving and greater ad-lib consumption.
Of critical importance to the current study was the influence of pharmacokinetic and pharmacodynamic processes on drinking behavior when both variables were included concurrently. It was hypothesized that the influence of pharmacokinetics on both urge to drink and ad-lib consumption would operate, at least in part, through SR. Ascending limb stimulant response was expected to mediate the relation between rate of change on the ascending limb of the BAC curve and drinking behavior. Specifically, it was hypothesized that a more rapid rise in BAC on the ascending limb would predict greater subjective stimulation, which, in turn, would predict increased craving and ad-lib

consumption. A slower decline in BAC on the descending limb was expected to lead to greater sedation, which was expected to lead to reduced craving and ad-lib consumption. If these hypotheses were confirmed, the results of the proposed study would greatly enhance our understanding of SR to alcohol, and its role as an endophenotype for the development of alcohol use disorders. Individual differences in BAC curves may represent a genetic risk factor for drinking problems and the development of alcohol use disorders. Furthermore, the results may provide insight into the development of effective prevention and treatment programs for problematic drinking and related disorders by identifying specific patterns of pharmacokinetics and SR that relate to risky drinking behaviors.

CHAPTER 2

METHOD

PARTICIPANTS

A total of 251 people were screened for enrollment, with 146 meeting eligibility criteria for participation. Participants were recruited throughout Arizona State University, Tempe campus and the surrounding area. In order to qualify for participation, an individual had to be between the ages of 21-30 and have consumed three drinks on at least one occasion per week over the last three months. As a result of the inclusion criteria, participants were not asked to consume more alcohol than they otherwise would. Individuals were also excluded from participation if they reported any contraindications to consuming alcohol including (1) a flushing response to alcohol, (2) current high risk for alcohol-related problems, 3) current or past participation in abstinence-oriented programs for alcohol problems, and for women, (4) pregnancy. Individuals who were screened out due to high risk for alcohol-related problems were contacted by phone and provided with information about their heightened risk, and were offered information about treatment services. Eligible participants were required to weigh less than 300 pounds, report no medical or other contraindications to alcohol use, and have no religious objections to consuming alcohol. Previous participants of studies conducted in our lab were also excluded from participation in the current study. Given that one of the dependent variables in the current study was the amount of beer consumed during a taste rating task, participants were screened for their preference for beer. Those who indicated that they disliked beer (e.g., those scoring 3 or less on a 10 point scale assessing how much they like beer), were excluded from the study. A total of 99 interested participants

were deemed ineligible for participation given the criteria listed above. Thirty-six participants did not meet the minimum drinking requirement; 34 reported at least one medical or other contraindication for alcohol use; 25 did not sufficiently like the taste of beer; two had participated in previous alcohol administration studies in our lab; one did not meet the weight requirement; and one fell outside of the age range for eligible participation. An additional six individuals were deemed ineligible due to excessively high alcohol consumption and were later contacted and provided with referrals for treatment services. The remaining 146 contact calls were determined to be eligible for participation, of these 39 were eligible but did not participate due to scheduling conflicts.

A total of 107 participants enrolled in the study and completed the protocol. As data collection commenced, it became apparent that the initial alcohol dosing procedure would not consistently reach a peak BAC of greater or equal to .08 g%. During the first few nights of data collection, several participants failed to reach a peak BAC greater than .06 g%. Furthermore, several participants achieved a peak BAC prior to the first measurement, essentially invalidating their ascending limb data. The decision was made to modify the dosing procedure by increasing the amount of alcohol consumed to reach a target BAC of .08 g%. Additionally, in order to slow the rate of absorption on the ascending limb, a weight adjusted snack of pretzels was provided to each participant to ensure similar stomach contents across participants. The new dosing procedure was implemented following IRB approval. The first eight participants who completed the study with the initial dosing protocol were not included in the following analyses. Thus, the final sample for analysis included 99 participants.

COMPENSATION

Participants were compensated with monetary payment based on the total amount of time spent in the lab, at the rate of $10 per hour. Participants were also recruited through introductory psychology classes at ASU. Students enrolled in introductory psychology classes at ASU are required to volunteer as a participant in research studies for a total of 6 hours or to fulfill an alternate requirement. The amount of time required for participation in the current study was roughly 5 to 7 hours. Psychology students enrolled in the study were awarded three research credits for partial fulfillment of their research requirement for the first three hours of study participation. Monetary compensation was provided at the rate of $10 per hour for the amount of time each participant was required to remain in the lab beyond the first three hours of participation. A total of ten introductory psychology students were enrolled in the current study.

PROCEDURES

Participants completed all study procedures in groups of 2-4. To ensure that participants reached target peak BACs in a uniform manner, they were instructed not to consume alcohol or any non-prescription drugs during the 24-hour period prior to the study, and not to eat for the 4-hour period prior to the study. Participants were informed that they would not be permitted to consume any tobacco products during data collection or to use nicotine replacement products (as some research suggests that alcohol increases craving for nicotine in dependent smokers; Shiffman et al., 1997; Zacny, 1990); however, participants were allowed to use tobacco products following the study protocol while they are waiting for their BAC to reach a safe level.

All participants were instructed to arrive at the lab at five o'clock in the evening on their scheduled day of data collection. When participants arrived in the lab, their age was verified via photo identification; and they were asked to read and sign a statement of informed consent. With the assistance of a female research assistant, female participants performed their own urine test for pregnancy, and signed a form stating that they completed the test and that the result was negative (not pregnant). None of the pregnancy tests administered during the current study resulted in a positive test. Participant height and weight was calculated in order to perform alcohol dosing calculations.

The experimental session included the completion of baseline behavioral measures and surveys followed by beverage administration in the bar laboratory. Baseline surveys and questionnaires were administered individually on computers located in a laboratory office space adjacent to the simulated bar lab. These assessments were used to gather information on individual differences in personality and behavioral control, subjective responses to alcohol, social desirability, drinking history and related problems. A list of baseline measures relevant to the analyses is provided below (see also Appendix A). Participants were encouraged to complete all items, but were informed that they may refuse to answer any items that they did not feel comfortable completing. Participants also completed an interview based measure of alcohol use (the Timeline Follow-back Interview; see descriptions below), and were asked to describe the type and quantity of the last food and beverages they consumed before entering the lab as well as the time of consumption. Self-report measures were administered via the web using surveymonkey.com. The self-report measures and interviews lasted approximately 1 hour. Participants also completed baseline measures of neuropsychological tests that

were re-administered following alcohol administration. The neuropsychological tests included the Finger Tapping Test and Trail Making Test (Christianson & Leathem, 2004; Tombaugh, 2004; Yochim, Baldo, Nelson, & Delis, 2007). The baseline neuropsychological tests took approximately 10-15 minutes to complete. Data from the neuropsychological tests are not relevant to the aims of the current study, and were not used in the analyses.

Beverage administration commenced after participants completed all initial surveys and tests. The first beverage was administered between 6:45pm and 7:15pm for all participants. Participants were escorted as a group into the simulated bar and received two beverages containing alcohol. Using standardized alcohol administration procedures, RAs calculated individual doses based on Curtin and Fairchild's (2003) formula which incorporates participant gender, age, height, and weight. Beverages were poured from vodka bottles in full view of participants. Participants were given 10 minutes to consume each of two beverages containing a 1:2 mixture of 80 proof vodka to mixer (cranberry juice and lime juice) to achieve a target BAC of .08%. Following a 10-minute absorption period, participants rinsed with alcohol free mouthwash to remove any residual alcohol, and their first post-administration BAC reading was taken. Protocol supervisors used handheld breathalyzers to assess participant's BAC every 10 minutes during the protocol to comprehensively measure changes in BAC over time. Once each participant recorded an ascending limb BAC of .06 g% or higher, they were asked to complete the ascending limb measures of subjective response and neuropsychological tests. Participants first completed the self-report measure of subjective response (BAES), followed by the neuropsychological tests. The ascending limb tasks took 10-15 minutes to complete.

Once participants recorded a descending limb BAC that was equivalent to their ascending limb BAC, they completed the descending limb measures of subjective response and neuropsychological tests in order to approximate the corresponding BAC measurements on the ascending limb. The order of tests was identical to the order used on the ascending limb. Participants first completed the self-report measure of subjective response (BAES), followed by the neuropsychological tests.

Upon completion of the descending limb measures of subjective response and neuropsychological tests, all participants were provided with an opportunity to consume two additional beverages that they believed contained alcohol. Participants were taken individually into a private room and informed that the research team was considering using beer instead of a mixed drink cocktail in a future lab-based study. They were told that the researchers were considering two different types of beer to be used in a future study, and they were asked to rate their preference for the two beers to assist the researchers. They were asked to taste a sample of each beer and rate their preference for the beverages along several dimensions, as well as indicate their preference for the beer in general. Participants were afforded 10 minutes to consume the beer and complete the taste-rating task. Participants were led to believe that the beverages were typical alcoholic beers; however, the beverages were non-alcoholic. The amount of beer consumed during this task served as one of the dependent variables in the study. The use of deception (telling participants that the non-alcoholic beer was an alcohol beer) was necessary to increase the likelihood that participants engaged in the task. The use of non-alcohol beer also minimized the amount of time participants were required to spend in the lab. Using alcoholic beer in the taste-rating task would cause BAC levels to rise and

increase the amount of time needed for participant BACs to fall below .03 g%. After each participant finished the taste-rating task, they were escorted back into the bar lab, and a research assistant measured the amount of beer remaining in milliliters.

Following completion of the taste-rating task, participants were provided with movies and games to occupy their time until their BAC dropped below .03 g% and they were able to leave. Participants were also provided with snacks and non-alcohol beverages. Participant BAC was assessed and recorded every 20 minutes following the protocol. In accordance with the National Institute on Alcohol Abuse and Alcoholism Guidelines for Ethyl Alcohol Administration in Human Experimentation, participants were be asked to remain in the laboratory until their BAC dropped to 0.03 g% (measured by breathalyzer tests) and their observed behavior returned to normal. Participants were then be debriefed (see Appendix 3), paid, and provided with transportation to their place of residence. Research credit hours were posted online within 24 hours of participation.

MEASURES

Screening Measure. A telephone screening questionnaire was used to collect demographic information including age and gender (See Appendix A). Medical and personal contraindications to the consumption of alcoholic beverages were assessed using items from the RAND dependence scale (Armor, Polich, & Stambul, 1978). Drinking habits were measured with a single item from the Daily Drinking Questionnaire (DDQ; Collins, Parks, & Marlatt, 1985), which asked respondents to indicate the typical number of drinks consumed on each day of a representative week during the past three months. Participants were also asked to rate their preference for beer using a scale from 1 to 10.

Participants who indicated that they disliked the taste of beer (3 or less on the rating scale) were excluded from the study.

Baseline Survey Measures.

Demographic Information. A single questionnaire assessed basic demographic information, including age, sex, ethnic/racial identity, educational background, academic standing, socio-economic status and disposable income.

Tobacco Use. The Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) is a 6-item measure of nicotine use and dependence, and was included based on research showing that the administration of alcohol leads to increased craving for nicotine among smokers (Shiffman et al., 1997; Zacny, 1990). The 6-item FTND produces a score between zero and ten indicating the severity of nicotine dependence. Participants are classified as having either no nicotine dependence (score of zero), low dependence (1-2), low to moderate dependence (3-4), moderate dependence (5-7), or high dependence (>8). Increased craving for nicotine under conditions of nicotine deprivation may lead to differences in subjective experiences following alcohol use. Thus, it is important to control for the effects of nicotine dependence on subjective alcohol effects. Nicotine dependence was included as a covariate in the primary analyses if it was found to be significantly related to predictor or outcome variables in the analyses.

***Food and Beverage Consumption*:** Although participants were instructed to refrain from eating during the four hours prior to their study appointment, the amount and type of food consumed during the last meal may influence the BAC

curves. In order to control for this potential confounding effect, participants were asked to describe all food and beverages consumed on the day that they participated in the lab study, including the time of consumption, type of food, and quantity (small, medium, or large portion). Amount consumed and time since last meal were included as a covariates in the analysis to control for differences in stomach contents that may impact alcohol absorption and metabolism.

Family History of Alcohol Problems. The Family Tree Questionnaire (FTQ; Mann, Sobell, Sobell, & Pavan, 1985) asks participants to use a rating scale to identify immediate biological family members who they perceive as current or past problem drinkers. Based on the participant's responses, stringent criteria can be applied to identify relatives with definite alcohol problems and less stringent criteria can be used to identify relatives with probable alcohol problems. Evidence for validity of the measure comes from research demonstrating a greater number of family history positive relatives among individuals with alcohol-related problems. Given the well-established relations between family history status and subjective response to alcohol (Grant, 1998), family history of alcohol problems was assessed as a potential confounding variable. Family history of alcohol problems was calculated using the participant's report of parental drinking habits. Positive family history of drinking problems was defined as having one or more parent who was identified as being a probable or definite problem drinker. While a family history of alcohol problems may be related to individual variability in both pharmacokinetics and SR, the scope of the current study and

modest sample size did not permit the examination of family history as a primary independent variable of interest.

Alcohol-Related Consequences. A 48-item questionnaire was used to assess the broad range consequences that may result from alcohol use (Young Adult Alcohol Consequences Questionnaire (YAACQ; Kahler, Strong, & Read, 2005; Read, Kahler, Strong, & Colder, 2006). The YAACQ includes questions regarding social/interpersonal consequences (e.g., "I have become very rude, obnoxious, or insulting after drinking alcohol."), academic/occupational consequences (e.g., "I have neglected my obligations to family, work, or school because of my drinking."), risky behaviors (e.g., "I have taken foolish risks when I have been drinking"), impaired control (e.g., "I often drink more than I originally had planned."), poor self-care (e.g., I have been less physically active because of my drinking"), diminished self-perception (e.g., "I have felt badly about myself because of my drinking."), blackout drinking (e.g., "I have awakened the day after drinking and found that I could not remember a part of the evening."), and psychological dependence (e.g., "I have felt anxious, agitated, or restless after stopping or cutting down on drinking."). Participants responded to each item with a "yes" or "no". Alcohol consequences, as measured by the YAACQ, were assessed to describe the drinking characteristics of the sample, but were not included in the primary analyses.

Baseline Interview Measures. The Timeline Follow-back Interview (TLFB; Sobell & Sobell, 1992) allows for retrospective assessment of alcohol use. An interviewer presented the participant with a 30-day calendar and asked for daily drinking

estimates during that period of time, including number of drinks consumed and duration of the drinking period. Participants were encouraged to view their day planners and personal calendars to identify important dates and facilitate recall of drinking episodes during the assessment period. The TLFB provides a measure of drinking frequency (number of drinking episodes), as well as drinking quantity for each episode and the time span over which each episode occurred. Previous research suggests that the TLFB has adequate test-retest reliability (r = .92) and is positively associated with other indices of drinking frequency/quantity. Data from the TLFB were used to calculate typical drinking variables, including typical weekly drinking and frequency of binge drinking (5 or more drinks during a drinking occasion for men; 4 or more drinks during a drinking occasion for women; (Knight et al., 2002). Typical weekly drinking (quantity/frequency) was included as a covariate in the analyses.

Post Drinking Survey Measures.

Subjective Response to Alcohol. The Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993) is a 14-item questionnaire comprising two sub-scales that assess subjective experiences of alcohol stimulation (e.g., energized, talkative) ($\alpha = .94$) and sedation (e.g. heavy head, slow thoughts) ($\alpha = .87$). Participants rated the extent to which they experienced each effect on 11-point Likert-type scales from not at all (0) to extremely (10). In the current study, the BAES was administered at baseline, and during the ascending and descending limb assessments.

Craving. The Alcohol Urge Questionnaire (AUQ) is an 8-item self-report questionnaire that assesses urge to have an alcoholic drink at the time of

questionnaire administration (Bohn, Krahn, & Staehler, 1995). The scale demonstrates high internal consistency and test-retest reliability and is highly correlated with measures of alcohol dependence severity. For the current study, the AUQ indicated high internal consistency on both the ascending ($\alpha = .83$) and descending limb ($\alpha = .83$).

Physiological Measures. Individual differences in blood alcohol curves served as the primary indicator of alcohol pharmacokinetics. BAC readings were measured by the PI or graduate research assistants every 10 minutes during the protocol using handheld breathalyzers (Alco-Sensor III; Intoximeters, Inc., St. Louis, MO). These regular intervals allowed for multiple BAC measurements during both the ascending and descending limbs of the blood alcohol curve, and for accurate calculations of several parameters that reflect individual differences in the pharmacokinetics of alcohol. Calculations included the amount of time needed to reach peak BAC, peak BAC, as well as area under the curve (AUC) on both the ascending and descending limbs. To calculate the respective AUC on the ascending and descending limbs of the BAC curve, we first calculated the total ethanol exposure which is defined as the area under the concentration-time curve estimated by the trapezoidal rule [$AUC_{0 \rightarrow \infty}$]. Ascending limb AUC was calculated in a similar manner with peak BAC as the endpoint [$AUC_{0 \rightarrow Tmax}$], whereas descending limb AUC was calculated with peak BAC as the start point [$AUC_{Tmax \rightarrow \infty}$]. The ascending and descending AUC calculations provide estimates of the amount of ethanol exposure during the absorption and metabolism stages.

Behavioral Measures. Ad-lib Consumption was measured as the amount of beer consumed during the beer taste rating task. We calculated the amount consumed by

measuring the amount of beer remaining in the glasses following the task and subtracting from the original amount provided to the participant (24 oz.; 710 ml).

CHAPTER 3

DATA ANALYTIC PLAN

Descriptive data analysis was conducted to examine the data prior to the primary analyses. Measures of central tendency and variability (means and standard deviations), as well as indications of skewness and kurtosis, were calculated for demographic variables and variables of primary interest. Frequency distributions were examined for demographic variables. To assess for possible covariates in the primary analyses, correlations were examined between possible covariates and both the predictor and outcome variables.

Previous research has suggested that SR varies according to limb of the BAC curve, with stronger stimulant effects on the ascending relative to descending limb, and more pronounced sedative effects on the descending limb relative to the ascending limb. To test this assumption, mean levels of subjective stimulation on the ascending and descending limb were compared using a paired samples t-test. Mean levels of subjective sedation on the ascending and descending limb were similarly compared.

Separate models were tested for ascending and descending limb measures, followed by models that included both ascending and descending limb pharmacokinetic and pharmacodynamic measures as simultaneous predictors of craving and ad-lib consumption using Mplus with maximum likelihood estimation. The first set of models assessed the effects of ascending limb measures (ascending AUC and SR) on the dependent variables of ascending limb craving (see Figure 3) and ad-lib consumption (see Figure 4). A subsequent ascending limb model included both craving and ad-lib consumption simultaneously, and assessed the indirect effects of AUC and SR on ad-lib

consumption operating through craving (see Figure 5). The second set of models assessed descending limb effects on the dependent variables of descending limb craving (see Figure 6) and ad-lib consumption (see Figure 7). Similar to the ascending limb model presented in Figure 5, a third descending limb model included both dependent variables, craving and ad-lib consumption (see Figure 8). These models allowed for examination of limb specific effects of pharmacokinetic and SR on both craving and ad-lib consumption. A final series of models included both ascending and descending limb effects. The addition of the descending limb effects to the first model allowed for the assessment of the influence of descending limb BAC rate of change and SR on craving and ad-lib consumption, while controlling for the ascending limb effects. Similar to the limb specific models, separate models were examined for both craving (assessed on the descending limb) and ad-lib consumption (Figures 9 and 10, respectively), as well as a full model with craving and ad-lib consumption included together (see Figure 11). The sequential ordering of the dependent variables in Figure 11 allowed for the examination of both the direct and indirect effects of subjective response (through craving) on ad-lib consumption as well as multiple mediator models of indirect effects of the BAC parameters on ad-lib consumption operating through both subjective response and craving. Direct and indirect effects were estimated using the bias corrected bootstrapping method in Mplus, following recommendations by MacKinnon (2008). The bias-corrected bootstrap method provides more accurate confidence intervals for the mediated effect, when the mediated effect is nonzero. See Table 1 for a summary of the variables included in each model.

The following general regression equation explicitly describes the model analyses that were conducted:

[1] $$\eta = B\eta + \Gamma\xi + \zeta$$

Where η is the vector of endogenous variables, ξ is the vector of exogenous variables, and ζ is the vector of residual variability. In the model, variable B represents the matrix of coefficients among the exogenous variables, and Γ represents the coefficients relating the exogenous to endogenous variables. Model 1 consisted of direct paths from the exogenous variable (ascending limb rate of change) to the three endogenous variables (stimulation, sedation, and craving assessed on the ascending limb). The model also included direct effects of stimulation and sedation on craving, and allowed for the examination of indirect effects of rate of absorption on craving through the subject response measures, stimulation and sedation. With this and all subsequent models all direct and indirect paths were estimated simultaneously using the bias corrected bootstrap method, which utilizes sampling with replacement to generate an empirical solution. Mplus provides estimates of the total indirect effects, as well as estimates of the specific indirect effects. It was hypothesized that the effect of rate of absorption on craving would be mediated by stimulation. Faster absorption (e.g. smaller ascending limb AUC) was expected to result in greater stimulation, which in turn was expected to lead to greater self-reported craving. Confidence intervals were examined to assess significant indirect paths. The proportion of the total effect that is mediated was calculated as a measure of the effect size of the total mediated effect.

The paths assessed in Model 2 were identical to those of Model 1, with the exception that subjective craving was replaced with ad-lib consumption. Similar to

Model 1, the second model assessed the direct effects of rate of absorption on subjective stimulation, sedation, and of ad-lib consumption. The direct effects of stimulation and sedation on ad-lib consumption were also assessed, as were indirect effects of rate of absorption on adlib consumption through the subject response measures, stimulation and sedation. It was hypothesized that effects of rate of change in BAC on the ascending limb would operate indirectly on ad-lib consumption, through stimulation. Faster rate of absorption, defined as a smaller area under the curve on the ascending limb, limb was expected to result in greater stimulation, which would then lead to increased ad-lib consumption.

Model 3 combined the first two models, and examined ascending limb direct and indirect effects on the two outcome variables, ascending limb craving and ad-lib consumption. This model allowed for the examination of indirect effects of ad-lib consumption by rate of absorption through subjective response and craving. It was hypothesized that faster absorption would lead to greater self-reported stimulation on the ascending limb, which would predict increased craving, and subsequently greater ad-lib consumption.

The paths assessed in Model 4 were similar to those of Model 1, with the exception that BACs and subjective response measures were assessed on the descending rather than ascending limb of the blood alcohol curve. Similar to Model 1, the fourth model assessed the direct effects of rate of metabolism on subjective stimulation, sedation, and craving. The direct effects of stimulation and sedation on craving were also assessed, as were indirect effects of rate of metabolism on craving through the subject response measures, stimulation and sedation. It was hypothesized that rate of change of

in BAC on the descending limb would indirectly effect descending limb craving, through sedation. Slower rate of metabolism on the descending limb was expected to result in greater sedation, which would then lead to reduced craving.

Model 5 differed from Model 4 in that subjective craving was replaced with ad-lib consumption. In this model, rate of metabolism was examined as a predictor of descending limb subjective response and ad-lib consumption. Descending limb subjective stimulation and sedation were also examined as direct predictors of ad-lib consumption. The indirect effect of rate of metabolism on ad-lib consumption was assessed through both descending limb subjective stimulation and sedation. Similar to Model 4, it was hypothesized that faster metabolism would predict less subjective sedation on the descending limb, which would promote greater consumption during the taste rating task.

Model 6 combined the previous two models, and examined descending limb direct and indirect effects on the two outcome variables, descending limb craving and ad-lib consumption. This model allowed for the examination of indirect effects of rate of metabolism on ad-lib consumption through subjective response and craving. It was hypothesized that faster metabolism would lead to reduced self-reported sedation on the descending limb, which would predict increased craving, and subsequently greater ad-lib consumption.

Model 7 combined measures assessed on the ascending and descending limbs of the BAC curve to examine relations between descending limb pharmacokinetics and SR while controlling for ascending limb effects. This model assessed the influence of individual differences in alcohol metabolism on changes in SR over time. It further

assessed whether change in SR from the ascending to descending limb predicted changes in subjective craving from the ascending to descending limb of the BAC curve. It was hypothesized that faster metabolism would be associated with a more rapid decline in sedation from the ascending to descending limb, and a less rapid decline in stimulation. Furthermore, it was hypothesized that individuals who lost sedative effects more quickly would maintain craving to a greater extent, as would those who retained more stimulant effects over time. Both change in stimulation and sedation were hypothesized to mediate the effect of metabolism on craving.

In Model 8, subjective craving from Model 7 was replaced by ad-lib consumption. Similar to Model 7, greater retention of stimulant alcohol effect across the BAC curve were expected to predict greater ad-lib consumption, as was a faster reduction in subjective sedation. It was further hypothesized that a faster metabolism would have an indirect influence on ad-lib consumption, through change in SR over time, with faster metabolism predicting larger decreases in sedative effects and smaller decreases in stimulant effects, which in turn would lead to greater consumption on the taste rating task.

The final model (Model 9) combined the previous two models to assess the indirect effect of rate of metabolism on ad-lib consumption, through change in subjective stimulation, sedation, and craving. It was hypothesized that faster metabolism would lead to greater retention of stimulant effects and a greater reduction in sedative effects, which would subsequently lead to increased retention of subjective craving, and increased consumption on the taste rating task.

POWER ANALYSIS

A Monte Carlo simulation study was carried out in Mplus to determine the sample size required to obtain sufficient power to detect the hypothesized effects. Estimates of population parameters were drawn from the existing literature, whenever estimates were available. Parameter estimates for craving on ad-lib consumption were large in size. Moderate to large effect sizes were estimated for ascending limb rate of change and descending limb rate of change on ascending limb stimulation and descending limb sedation, respectively. Moderate effect sizes were estimated for ascending stimulation, descending sedation, and ascending rate of change on ad-lib consumption. All other paths were estimated as small to moderate in magnitude. Based on these parameter estimates, the Monte Carlo simulation carried out 10,000 replications of samples of size N=100. Results of the power analysis suggest that the proposed sample size would provide sufficient power to detect all of the hypothesized effects, with power greater than .80.

CHAPTER 4

RESULTS

DESCRIPTIVE STATISTICS

Approximately two-thirds of the final sample were men (men = 67; women = 31), with a mean age of 22.3 years (*SD* = 1.75). The vast majority of participants identified as White or Caucasian (n = 77; 80.2%) (see Table 2). Five participants identified as Asian (5.1%), three as Black or African-American (3.1%), and three as American Indian/Alaskan Native (3.1%). Eight participants selected "Other" for their racial identity (8.2%). With respect to ethnicity, fifteen participants (15.2%) identified as "Hispanic/Latino" (see Table 3).

All but five participants were enrolled as undergraduate (*n* = 89) or graduate (*n* = 4) students at the time of participation. The mean estimated annual family income for all participants was between $70-80,000. A quarter of participants had estimated annual family incomes below $50,000 and a quarter indicated estimated annual family incomes greater than $100,000, suggesting that the majority of participants came from middle to upper middle class households (see Table 3).

Regarding drinking history, participants were largely moderate to heavy social drinkers (see Table 2). Non-drinkers and potential problem drinkers were excluded from the study. The mean age of first alcohol consumption was 15.94 years (*SD* = 2.55; range: 5-22). The mean age of first self-reported intoxication due to alcohol use was 16.44 years (*SD* = 2.35; range: 10-22). Participants reported consuming an average of 40.29 (*SD* = 31.82; range: 1-150) standard alcoholic drinks during the past month, on a mean of 8.42 (*SD* = 4.98; range: 1-27) drinking days, which corresponds to an average of 4.80

(*SD* = 2.73) drinks per drinking day. Participants reported an average of 3.90 (*SD* = 3.50) binge drinking episodes during the month prior to participation (calculated as 5 or more drinks per drinking episode for men, and 4 or more drinks per drinking episode for women; range: 0-15). Over one third of participants (36.7%) were classified as having a positive family history of alcohol problems, calculated as having one or more biological parent who is a definite or probable problem drinker. The majority of participants did not smoke cigarettes (83.7%).

Participants obtained a mean peak BAC (C_{max}) of .087 g% (*SD* = .013), with a mean time to peak (T_{max}) of 63.16 minutes (*SD* = 20.29). Peak BAC ranged from .061 to .116 g% during the course of the study. The mean BAC recorded at the ascending limb measurement was .074 g% (*SD* = .013), compared to .071 g% (*SD* = .011) on the descending limb. See Table 5 for descriptive statistics for all pharmacokinetic measures.

IDENTIFICATION OF COVARIATES

Conventional demographic/background variables including age, gender, and ethnicity can operate as confounding variables that can influence the association between the proposed predictors and the outcome variables of interest. Family history of alcohol problems was also assessed as a possible covariate given well-established relations between family history status and subjective response to alcohol (Schuckit, 2002, 2009), as well as typical drinking behaviors (e.g., age of first use, average weekly consumption) (Chassin, Mann, & Sher, 1988; Grant, 1997; Sher, Walitzer, Wood, & Brent, 1991; Warner, White, & Johnson, 2007). A correlational analysis was conducted to examine relations between the potential covariates and both the predictor and outcome variables of primary interest. Potential covariates that were found to significantly relate to the

variables of primary interest were included in analyses designed to test the primary study hypotheses. Correlational analyses indicated that participant sex was significantly correlated with rate of metabolism ($p = .001$) and amount of beer consumed during the taste rating task ($p = .001$). Women metabolized alcohol more quickly than men, and male participants consumed more beer on the taste rating task. Typical number of drinks per drinking day was significantly correlated with ad-lib consumption ($p < .001$), with individuals who drank more heavily during the month prior to participation consuming more beer during the taste rating task.

A total of 16 participants identified as cigarette smokers in the current study (16.3%). Of the participants who smoked, three were classified as having low nicotine dependence (18.8% of smokers), and the remaining were classified as having low to moderate dependence. Level of nicotine dependence was significantly correlated with sedation on both the ascending ($p = .003$) and descending limb ($p = .006$), with higher levels of nicotine dependence associated with greater sedation on both limbs.

Participant age was not significantly correlated with any of the predictor or outcome variables. Due to the relatively small number of racial and ethnic minority participants, a dichotomous variable was created to assess the correlation between race and the predictor and outcome variables. Participants were classified as either Caucasian or other racial/ethnic group. The binary race variable was not significantly correlated with any of the predictor or outcome variables, but was significantly correlated with typical drinking behavior ($p = .024$), with Caucasian participants consuming more on a typical drinking day than non-Caucasian participants.

A positive family history of alcohol problems was significantly correlated with self-reported sedation on the descending limb (p =.05). Participants with a positive family history of alcohol problems reported less sedation as blood alcohol levels were falling.

As expected, beer preference was significantly correlated with amount consumed on the taste rating task (p = .003), with individuals who had a greater preference for beer consuming more beer. See Table 6 for correlations between all predictors, outcomes, and potential covariates.

Based on the results of the correlational analyses, participant sex and typical drinks per drinking day were controlled for in relation to the outcome variable of ad-lib consumption. Nicotine dependence was controlled for when predicting self-reported sedation on both the ascending and descending limb of the BAC curve. We further controlled for family history of alcohol problems for analyses examining self-reported sedation on the descending limb as an outcome. Because beer was the beverage utilized in the taste rating task, participant preference for beer was controlled for in the prediction of amount consumed during the taste rating task.

Participants were instructed to refrain from eating for four hours prior to the beginning of the study to control for stomach contents prior to beverage administration; however, meal size of the last meal consumed was also statistically controlled for in relation to both ascending and descending limb AUCs. As pharmacodynamic processes may be influenced by the total concentration of ethanol in addition to the rate of at which ethanol is absorbed and metabolized, we controlled for ascending limb BAC on SR for

ascending limb only models (Models 1 through 3) and descending limb BAC on SR for all models that included descending limb measurements.

ASSESSING BIPHASIC EFFECTS OF SUBJECTIVE RESPONSE: DIFFERENCES IN SR BETWEEN THE ASCENDING AND DESCENDING LIMB

A series of paired samples t-tests were conducted to determine whether the subjective response experienced by participants differed across the ascending and descending limb of the BAC curve. Results indicated a significant difference in subjective stimulation by limb, $t(97) = 5.946$, $p < .001$. Greater stimulation was reported on the ascending limb of the BAC curve ($M = 5.54$; $SD = 1.97$) relative to the descending limb ($M = 4.61$; $SD = 1.96$). No significant differences were evident for subjective sedation measured on the ascending limb ($M = 2.15$; $SD = 1.50$) and the descending limb ($M = 2.25$; $SD = 1.77$), $t(97) = -.678$, $p = .499$. The difference between subjective craving measured on the ascending and descending limbs was significant, $t(95) = 5.507$, $p < .001$. Greater subjective craving was evident on the ascending limb ($M = 3.38$; $SD = 1.19$) compared to the descending limb ($M = 2.84$; $SD = 1.13$).

ASSESSING ASCENDING LIMB EFFECTS IN ISOLATION

The first model assessed the influence of rate of absorption on subjective stimulation and sedation, and relations between these measures of SR and craving, as assessed on the ascending limb (see Figure 3). Rate of absorption was inferred by the area under the BAC from initial consumption to peak BAC for each participant. Results of the model indicated a good overall fit to the data, $\chi^2(7) = 5.831$, $p = .560$, CFI = 1.00, RMSEA = .000, SRMR = .042. While the model fit the data well, none of the model

parameters were significant. Rate of absorption did not significantly predict subjective stimulation (β = .006, p = .963), sedation (β = -.039, p = .726), or craving (β = -.009, p = .923) on the ascending limb. In addition, the influence of subjective stimulation on craving during the ascending limb was not significant (β = .177, p = .110). The influence of ascending limb sedation on subjective craving was also not significant (β = .057, p = .634). See Figure 13 for a path diagram of the results for Model 1. None of the indirect effects of rate of absorption on craving were significant. See Table 8 for a summary of the specific indirect effects in Model 1.

The second model assessed the influence of rate of absorption on subjective stimulation and sedation and the effects of these SR measures on ad-lib consumption (see Figure 4). Results of the model indicated a good overall fit to the data, $\chi^2(17) = 15.889$, p = .532, CFI = 1.00, RMSEA = .000, SRMR = .053. Consistent with the results of Model 1, rate of absorption did not significantly predict subjective stimulation (β = .006, p = .963) or sedation (β = -.039, p = .725), nor did it predict ad-lib consumption (β = -.032, p = .718) on the descending limb. Neither subjective stimulation (β = .045, p = .611), nor sedation (β = .037, p = .629) assessed on the ascending limb was associated with ad-lib consumption on the descending limb. See Figure 14 for a path diagram of the results for Model 2. None of the indirect effects of rate of absorption on ad-lib consumption were significant. See Table 9 for a summary of the specific indirect effects in Model 2.

Model 3 assessed the influence of rate of absorption on subjective stimulation and sedation on the ascending limb of the BAC curve, as well as the respective influence of these parameters on subjective craving and ad-lib consumption. Results of the model indicated a good overall fit to the data, $\chi^2(22) = 21.479$, p = .491, CFI = 1.00, RMSEA =

.000, SRMR = .053; however, none of the paths in the model were significant. Rate of absorption did not significantly predict subjective stimulation (β = .006, p = .963), sedation (β = -.039, p = .727), or craving (β = -.009, p = .924) on the ascending limb. Furthermore, rate of absorption did not significantly predict amount consumed on the taste rating task (β = .040, p = .667). The influence of subjective stimulation on craving during the ascending limb approached significance (β = .177, p = .112), with a trend for greater stimulation predicting more craving. The influence of ascending limb sedation on subjective craving was not significant (β = .057, p = .637). Neither stimulation (β = .009, p = .921) nor sedation (β = .026, p = .788) measured on the ascending limb significantly predicted ad-lib consumption. Ascending limb craving did not significantly predict amount of beer consumed on the taste rating task, though the effect approached significance (β = .164, p = .076), with a trend for greater craving predicting more ad-lib consumption. See Figure 15 for a path diagram of Model 3. Consistent with the previous two models, none of the indirect effects of rate of absorption on ad-lib consumption, through subjective stimulation, sedation, or craving were significant. See Table 10 for a summary of the specific indirect effects in Model 3.

ASSESSING DESCENDING LIMB EFFECTS IN ISOLATION

Model 4 assessed the influence of rate of metabolism on subjective stimulation and sedation on the descending limb of the BAC curve, as well as the respective influence of these parameters on subjective craving, which was also measured on the descending limb. Rate of metabolism was inferred by the area under the BAC curve following peak BAC for each participant. Results of the model indicated an adequate overall fit to the data, $\chi^2(13) = 17.206$, p = .190, CFI = .886, RMSEA = .057, SRMR =

.052. Rate of metabolism significantly predicted subjective stimulation (β = -.290, p = .004). Individuals who metabolized alcohol more quickly reported greater subjective stimulation on the descending limb. The rate at which alcohol was metabolized did not, however, significantly predict subjective sedation (β = .103, p = .360), or craving (β = -.032, p = .777) on the descending limb. Neither subjective stimulation (β = .128, p = .226) nor sedation (β = .014, p = .907) measured on the descending limb predicted descending limb craving. See Figure 16 for a path diagram of the results for Model 4. Model 4 assessed indirect effects from rate of metabolism to self-reported craving through subjective stimulation and sedation. None of the indirect effects of rate of metabolism on craving were significant. See Table 11 for a summary of the specific indirect effects in Model 4.

Model 5 assessed the influence of rate of metabolism on subjective stimulation and sedation on the descending limb of the BAC curve, as well as the respective influence of these parameters on ad-lib consumption. Results of the model indicated a good overall fit to the data, $\chi^2(19) = 22.590$, p = .256, CFI = .939, RMSEA = .044, SRMR = .053. Consistent with the results of Model 4, rate of metabolism significantly predicted subjective stimulation (β = -.291, p = .004). Individuals who metabolized alcohol more quickly reported greater subjective stimulation on the descending limb. The rate at which alcohol was metabolized did not significantly predict subjective sedation (β = .103, p = .360), or amount consumed during the taste rating task (β = -.065, p = .596). Subjective sedation measured on the descending limb did not predict ad-lib consumption (β = -.119, p = .215). Subjective stimulation, however, did significantly predict ad-lib consumption (β = .203, p = .039). Participants who endorsed greater

subjective stimulation on the descending limb of the BAC curve consumed a greater amount of beer during the taste rating task. See Figure 17 for a path diagram of the results for Model 5. Although rate of metabolism did not directly influence ad-lib consumption, results of the mediation analysis indicated that the total indirect effect of metabolism on ad-lib consumption approached significance (β = -.071, 90% CI [-.138, -0.005]). The total indirect effect accounts for the indirect effects of rate of metabolism on ad-lib consumption through both stimulation and sedation. The specific indirect path for rate of metabolism on ad-lib consumption through subjective stimulation was not significant (β = -.059, 95% CI [-.134, .016]), but accounted for 80.8% of the total indirect effect. While not significant, this finding suggests that participants who metabolized alcohol at a faster rate experienced more stimulation on the descending limb, which promoted increased consumption on the taste rating task. The indirect effect through sedation on ad-lib consumption was also not significant (β = -.012, 95% CI [-.048, .024]). See Table 12 for a summary of the specific indirect effects in Model 5.

Model 6 assessed the influence of rate of metabolism on subjective stimulation and sedation on the descending limb of the BAC curve, as well as the respective influence of these parameters on descending limb craving and ad-lib consumption. Results of the model indicated a good overall fit to the data, $\chi^2(25) = 29.239$, p = .254, CFI = .937, RMSEA = .042, SRMR = .053. Consistent with the results of the previous models, rate of metabolism significantly predicted subjective stimulation (β = -.291, p = .004), with individuals metabolizing alcohol more quickly reporting greater subjective stimulation on the descending limb. The rate at which alcohol was metabolized did not significantly predict subjective sedation (β = .103, p = .356), descending limb craving (β

= -.031, p = .780), or amount consumed during the taste rating task (β = -.047, p = .685). Subjective sedation measured on the descending limb did not predict descending limb craving (β = .014, p = .780), or ad-lib consumption (β = -.117, p = .212). Subjective stimulation measured on the descending limb of the BAC curve did not significantly predict craving (β = .129, p = .221) or ad-lib consumption when craving was included in the model, though the effect on ad-lib consumption approached significance (β = .159, p = .100), with greater stimulation predicting greater ad-lib consumption. Craving measured on the descending limb significantly predicted ad-lib consumption (β = .267, p = .002). Participants who endorsed more craving on the descending limb of the BAC curve consumed larger amounts of beer on the taste rating task. See Figure 18 for a path diagram of the results for Model 6. None of the indirect effects in Model 6 were significant (see Table 13 for a summary of the specific indirect effects in Model 6).

FULL MODEL ASSESSING ASCENDING AND DESCENDING LIMB EFFECTS

The final set of models combined both ascending and descending limb effects, allowing for the examination of descending limb effects on craving and ad-lib consumption, while controlling for effects assessed on the ascending limb. Model 7 assessed ascending and descending limb pharmacokinetics in relation to subjective response, and the influence of these measures on subjective craving. Results of the model indicated a good overall fit to the data, $\chi^2(44) = 53.789$, p = .148, CFI = .953, RMSEA = .048, SRMR = .067. Participants who experienced greater stimulation on the ascending limb experienced greater stimulation on the descending limb as blood alcohol levels declined (β = .681, $p < .001$). A similar pattern of subjective response to alcohol from the ascending to descending limb was evident for sedation (β = .658, $p < .001$), with

greater sedation on the ascending limb predicting greater sedation on the descending limb. Individuals who reported greater subjective craving on the ascending limb also reported greater craving on the descending limb (β = .661, p < .001). Participants who metabolized alcohol more quickly maintained greater stimulation from the ascending to descending limb of the BAC curve (β = -.228, p = .007). Participants who metabolized alcohol more quickly also appeared to lose sedative effects more quickly; however, this effect did not reach statistical significance (β = .149, p = .090). Consistent with Model 4, descending limb craving was not significantly predicted by rate of metabolism (β = -.078, p = .364), stimulation (β = .012, p = .882), or sedation (β = -.055, p = .550). See Figure 19 for a path diagram of the results for Model 7.

Model 7 evaluated the indirect effects of rate of metabolism on craving through change in subjective stimulation and sedation from the ascending to descending limb. Consistent with Models 3, there was no evidence of significant indirect effects operating through either stimulation or sedation. See Table 14 for a summary of the specific indirect effects in Model 7.

Model 8 assessed ascending and descending limb pharmacokinetics and subjective response in relation to ad-lib consumption, which allowed for the examination of descending limb effects on ad-lib consumption, while controlling for effects assessed on the ascending limb. Results of the model indicated a good overall fit to the data, $\chi^2(45) = 53.522$, p = .180, CFI = .952, RMSEA = .044, SRMR = .066. Consistent with Model 7, participants who metabolized alcohol more quickly maintained greater stimulation from the ascending to descending limb of the BAC curve (β = -.228, p = .002). Participants who metabolized alcohol more quickly also appeared to lose sedative

effects more quickly; however, this effect did not reach statistical significance (β = .149, p = .057). Individuals who maintained greater stimulation from the ascending to descending limb of the BAC curve consumed a greater amount during the ad-lib consumption period (β = .269, p = .033). Participants who experienced a greater decrease in subjective sedation from the ascending to descending limb also appeared to consume a greater amount during the taste rating task; however, this effect did not exceed the traditional threshold for establishing statistical significance (β = -.202, p = .095). See Figure 20 for a path diagram of the results for Model 8.

Model 8 assessed for potential indirect effects of rate of metabolism on ad-lib consumption through change in subjective stimulation and sedation from the ascending to descending limb of the BAC curve. The total indirect effect of rate of metabolism on ad-lib consumption was significant (β = -.091, 95% CI [-.172, -.011]). The specific indirect effect of metabolism on ad-lib consumption through stimulation approached statistical significant (β = -.061, 90% CI [-.118, -.004]), and accounted for 67% of the total indirect effect of rate of metabolism on ad-lib consumption. Although not significant, the results suggest that participants who metabolized alcohol more quickly retained more stimulation from the ascending to descending limb of the BAC curve, which subsequently led to greater consumption on the taste rating task. Similarly, the specific indirect effect of descending limb sedation did not exceed the traditional cutoff for statistical significance (β = -.030, 90% CI [-.069, .009]), but accounted for 33% of the total indirect effect of rate of metabolism on ad-lib consumption. Those who metabolized alcohol more quickly appeared to lose sedative effects at a faster rate, which in turn promoted greater consumption on the taste rating task. Although neither specific indirect

effect was significant, the significant total indirect effect of rate of metabolism on ad-lib consumption suggests that a faster rate of metabolism influences amount consumed within session by having the combined effect of maintaining greater stimulation and eliminating sedative effects more rapidly. See Table 15 for a summary of the specific indirect effects in Model 8.

The final model (Model 9) combined the previous two models to assess the effects of both ascending and descending limb pharmacokinetics on change in subjective response, and the respective influence of change in SR on craving and ad-lib consumption. Results of the model indicated a good overall fit to the data, $\chi^2(64) = 73.530$, $p = .194$, CFI = .960, RMSEA = .039, SRMR = .067. Consistent with the previous two models, participants who metabolized alcohol more quickly maintained greater stimulation from the ascending to descending limb of the BAC curve ($\beta = -.227$, $p = .002$). Participants who metabolized alcohol more quickly also appeared to lose sedative effects more quickly; however, this effect did not reach statistical significance ($\beta = .153$, $p = .057$). Consistent with Model 7, descending limb craving was not significantly predicted by rate of metabolism ($\beta = -.077$, $p = .354$), stimulation ($\beta = .012$, $p = .882$), or sedation ($\beta = -.055$, $p = .481$). Craving on the descending limb continued to predict ad-lib consumption after controlling for ascending limb craving ($\beta = .292$, $p = .012$). Participants who maintained greater craving from the ascending limb to the descending limb of the BAC curve consumed more beer on the taste rating task compared to those who showed larger decreases in craving over time. After controlling for ascending limb stimulation and craving, descending limb stimulation did not significantly predict ad-lib consumption ($\beta = .197$, $p = .111$). Descending limb sedation did, however,

significantly predict ad-lib consumption after controlling for ascending limb sedation and craving (β = -.233 p = .047). Participants who maintained more sedation over the course of the study consumed less beer on the taste rating task than those who reported greater decreases in sedative effects. See Figure 21 for a path diagram of the results for Model 9.

Potential indirect effects of rate of absorption and metabolism on both craving and ad-lib consumption through change in subjective stimulation and sedation were also assessed. The total indirect effect of rate of metabolism on ad-lib consumption was significant (β = -.105, 95% CI [-.196, -.014]), and accounted for over 80% of the total effect. These results suggest that, although there is no direct relationship between rate of metabolism and within session consumption, individuals who metabolized alcohol more quickly consumed more during the taste rating task indirectly through their subjective response. While the total indirect effect was significant, none of the specific indirect effects exceeded statistical thresholds for significance. The indirect effect of metabolism on ad-lib consumption through craving accounted for 22% of the total indirect effect (β = -.023, 95% CI [-.073, .028]). The indirect effect of metabolism on ad-lib consumption through stimulation accounted for 43% of the total indirect effect (β = -.045, 95% CI [-.107, .017]). The indirect effect of metabolism on ad-lib consumption through sedation accounted for 33% of the total indirect effect (β = -.035, 95% CI [-.083, .014]). Although none of the specific indirect effects of rate of metabolism were significant, each accounted for a sizable proportion of the total indirect effect. These results suggest that rate of metabolism influences the amount of alcohol one consumes by impacting subjective response. Individuals who metabolized alcohol more rapidly appeared to retain more stimulation and less sedation, which promoted greater consumption during

the taste rating task. See Table 16 for a summary of the specific indirect effects in Model 9.

CHAPTER 5

DISCUSSION

Alcohol misuse remains a pervasive problem in the United States, and is associated with a myriad of personal, social, and societal consequences. Although problematic drinking occurs across all age demographics from early adolescence, the highest proportion of alcohol related injuries and deaths occur during late adolescence and emerging adulthood (Meropol, Moscati, Lillis, Ballow, & Janicke, 1995; NHTSA, 2012). It is also within this age range that the highest rates of alcohol use disorders occur (Bachman, Wadsworth, O'Malley, Johnston, & Schulenberg, 1997; Grant, Dawson, Stinson, Chou, Dufour, & Pickering, 2004). While the majority of emerging adults with alcohol use disorders spontaneously remit from alcohol dependence as they enter adulthood, others continue to consume alcohol at dangerous levels (Chassin, Flora, & King, 2004; Dawson, Grant, Stinson, Chou, Huang, & Ruan, 2006; Jackson, Sher, Gotham, & Wood, 2001; Zucker, Fitzgerald, & Moses, 1995). Indeed, problematic drinkers in adolescence and early adulthood are more likely to maintain or progress to alcohol dependence later into adulthood (Bonomo, Bowes, Coffey, Carlin, & Patton, 2004). As such, it is necessary to identify protective and risk factors for problematic drinking during this critical period of emerging adulthood in order to prevent both the acute consequences of heavy alcohol use and the continuation of disordered drinking behaviors across the lifespan.

One promising predictor of alcohol related consequences and alcohol use disorders is the subjective response one experiences when consuming alcohol. Variability in subjective response to alcohol has been found to predict the amount

consumed within a single drinking session (King et al., 2002), and longitudinally predicts the development and persistence of alcohol dependence (King et al., 2011; Schuckit, 1994; Schuckit & Smith, 2000; Trim, Schuckit, & Smith, 2009). Subjective response to alcohol also appears to be heritable, with individuals with a positive family history of alcoholism experiencing a pattern of response to alcohol that differs from those without a family history of the disorder (Heath et al., 1999; Schuckit, 1980, 2009). This apparent heritability of SR to alcohol as well as its ability to predict future drinking behavior and problems has led some to speculate that SR may represent an endophenotype, or vulnerability marker, for alcohol use disorders (Ray et al., 2010; Morean & Corbin, 2010; Quinn & Fromme, 2011). Establishing SR as an endophenotype of alcoholism risk would provide many benefits in terms of both the identification and treatment of alcohol use disorders. Easily identified biobehavioral risk markers, such as an individual's SR profile, could inform prevention programs that are highly tailored, thus improving the effectiveness of the intervention.

The potential utility of SR as an endophenotype for alcohol use disorders is compelling. Before this relationship can be established, however, several questions remain to be answered. In order for SR to be a reliable indicator of genetic risk for alcohol use disorders, the pattern of response that confers risk must be more clearly elucidated. Linking SR to objective, physiological processes would provide further support for its role as an endophenotype of alcohol use disorders. Effective endophenotypes should have biological plausibility, that is, they should inform neurobiological and genetic factors that underlie alcohol use disorders (Tsuang, Faraone, & Lyons, 1993). The current study aimed to establish biological plausibility for SR by

assessing whether the SR one receives following a dose of alcohol is impacted by variability in pharmacokinetics.

If subjective response to alcohol is an endophenotype of problematic alcohol use, then the subjective experience one receives should relate to objective, physiological processes (Ray et al., 2010). As noted earlier, subjective response to alcohol represents an interpretation of the interoceptive cues following consumption that result from the pharmacodynamic properties of ethanol (Lees, Landoni, Giraudel, & Toutain, 2004; Ramchandani et al., 2001; Ray et al., 2010). Considerable research has identified genetic polymorphisms related to the pharmacodynamics of alcohol that contribute to SR following alcohol consumption. Specifically, variants of the mu opioid gene (OPRM1) have been found to relate to stimulant response , while the $GABA_A$ neurotransmitter relates to sedation (Anton, Voronin, Randall, Myrick, & Tiffany, 2012; Fromme et al., 2004; Ray & Hutchison, 2004; Schuckit et al, 1999). Genetic polymorphisms of the serotonin transporter have also been identified as contributing to a low level of response to sedative effects (Schuckit et al., 1999), and greater acute tolerance to subjective intoxication (Corbin, Fromme, Bergeson, 2006). While subjective response is primarily an interpretation of alcohol pharmacodynamics, the intensity and duration of the subjective experience is largely determined by alcohol pharmacokinetics. Establishing a relationship between alcohol pharmacokinetics and subjective response to alcohol would provide additional support for SR as an endophenotype for alcohol use disorders, and would provide an objective biomarker to infer risk (Ray et al., 2010).

To test this hypothesis, the current study examined variability in absorption and metabolism following consumption of a moderate dose of alcohol and the extent to which

individual differences in these pharmacokinetic parameters influence subjective response. It was hypothesized that faster absorption would lead to greater subjective stimulation as blood alcohol levels rose, and faster metabolism would predict less subjective sedation as blood alcohol levels declined. Results indicated that the rate at which alcohol was absorbed was not related to either stimulation or sedation; however, rate of metabolism was associated with subjective stimulation on the descending limb. Individuals who metabolized alcohol more quickly experienced significantly more stimulation on the descending limb, and maintained greater stimulation from the ascending to descending limb. Partial support was also provided for the relation between metabolism and descending limb sedation. Participants who metabolized alcohol more quickly experienced greater acute tolerance to sedative effects.

Although several studies have found evidence linking SR to drinking outcomes, the results of these studies are often conflicting (Morean & Corbin, 2010; Quinn & Fromme, 2011). While some studies suggest that an attenuated SR predicts drinking related consequences (Schuckit, 2004; Schuckit & Smith, 2000; Schuckit & Tipp, 1997), others report that a heightened response to some aspects of SR and a lower response to others is most predictive of disruptive drinking behaviors (Earleywine, 1995; King et al., 2002; Marczinski et al., 2007; Thomas, Drobes, Voronin, & Anton, 2004). Accordingly, the current study aimed to examine the relation between SR and within session drinking behavior. As the type of subjective response experienced during a drinking session varies according to the limb of the BAC curve (Newlin & Thomson, 1990), SR and its relation to drinking outcomes was assessed on both the ascending and descending limb.

Consistent with previous research (Earleywine & Martin, 1993; Erblich et al., 2003; King et al., 2002, 2011; Martin et al., 1993; Newlin & Thomson, 1990), greater stimulation was reported on the ascending limb compared to the descending limb of the BAC curve. Contrary to results of previous research, however, there was not a significant difference in sedation on the ascending versus descending limb (Earleywine & Martin, 1993; Erblich et al., 2003; Martin et al., 1993). It was hypothesized that greater subjective stimulation on the ascending limb would predict greater craving and within session alcohol consumption. This hypothesis was not supported; however, there was a trend for greater stimulation to predict increased craving. Interestingly, greater stimulation on the descending limb did predict greater ad-lib consumption during the taste rating task.

These results suggest that, although stimulant effects are more pronounced on the ascending limb, stimulant effects on the descending limb may be more likely to influence drinking behavior as blood alcohol levels are falling. One possible explanation for the null finding in regard to the relation between ascending limb stimulation and ad-lib consumption is that ascending limb measures were assessed roughly an hour before the taste rating task which occurred on the descending limb. As the taste rating task was administered on the descending limb of the BAC curve, descending limb stimulation may be more predictive of amount consumed simply due to the proximity of the measurement to the ad-lib consumption period. Since ad-lib consumption was not assessed on the ascending limb, it is impossible to know if greater stimulation on the ascending limb would relate to greater consumption if participants were allowed to engage in the taste rating task as blood alcohol levels were rising. However, participants who reported

greater stimulation on the ascending limb of the BAC curve were more likely to report higher levels of stimulation on the descending limb. Additionally, those who retained greater stimulation across the entire BAC curve also consumed more during the ad-lib taste rating task.

Regarding sedative alcohol effects, it was hypothesized that less subjective sedation on the descending limb would predict greater craving and within session alcohol consumption. Results indicated that sedative effects were not significantly associated with craving on either the ascending or descending limb; however, partial support was indicated for the association between descending limb sedation and ad-lib consumption. Although a reduced response to sedative effects on the descending limb did not, in and of itself, predict ad-lib consumption, a greater decrease in sedation from the ascending to the descending limb did predict greater consumption during the taste rating task. These results suggest that the potential influence of sedative effects on within session drinking behavior is less dependent on the limb of the BAC curve, and more related to the amount of acute tolerance experienced from the ascending to descending limb.

Considerable variability has been observed in alcohol pharmacokinetics (Norberg et al., 2003; Ramchandani et al., 2001), and individual differences in the pharmacokinetics of alcohol may influence drinking behavior. The majority of alcohol administration studies, however, fail to account for variability in absorption and metabolism, and instead control for some pharmacokinetic parameters (e.g., peak BAC) or ignore them altogether. As is illustrated in Figure 22, substantial variability was observed in participant BAC curves over the course of the study, in terms of both absorption and metabolism. Although absorption and metabolism did not influence

drinking behavior directly, the rate at which alcohol was metabolized did impact the amount consumed indirectly by modifying the subjective experience of alcohol as blood alcohol levels declined. Individuals who metabolized alcohol more quickly retained more stimulation and craving from the ascending to descending limb of the BAC curve, and experienced a more rapid reduction in sedative effects. This subjective response profile was associated with increased consumption during the taste rating task.

It is important to note that there was no evidence for relations between subjective response to alcohol and self-reported craving, despite the fact that both were related to ad-lib consumption. While SR and craving are related constructs, the respective influence of these constructs on drinking related decisions and behaviors may be distinct. The incentive sensitization theory of addiction proposes that repeated exposure to a potentially addictive drug alters brain cells and circuits that normally regulate the incentive salience of a stimulus (Robinson & Berridge, 2003). In other words, the neurological adaptations that result from drug use cause the individual to become hypersensitive to the drug and drug-related stimuli. Animal and human studies that have investigated the neural adaptations that result from continued drug use indicate that a heightened sensitivity from drug use mediates the reward system for motivation to use the drug (i.e, craving), but not the pleasurable effects of drug (i.e., subjective euphoria) (Berridge & Robinson, 1998; Robinson & Berridge, 2003). The theory of incentive salience may help explain why SR and craving were not related in the current study, but produced an additive rather than mediated effect on ad-lib consumption.

THEORETICAL IMPLICATIONS

The results of the current study regarding both stimulant and sedative effects cast doubt on current theories of SR, which emphasize limb specific influences of SR. The LLR model endorsed by Schuckit (1980; 2009) proposes that a lower SR to alcohol measured on the descending limb is most indicative of problematic drinking. While partial support for the LLR model was indicated in the current study regarding sedative effects the finding that greater stimulant effects on the descending limb predicted greater ad-lib consumption is incompatible with the LLR model. The results of the current study are more consistent with the differentiator model, which posits that a SR profile of high stimulation and low sedation is most predictive of drinking related problems. However, the emphasis of the differentiator model on the biphasic nature of SR, namely that stimulation is more predictive of drinking problems on the ascending limb of the BAC curve and sedation more predictive on the descending limb, was not supported in this study.

Recently, it has been proposed that a modification of existing theories of SR is necessary. A study by King and colleagues (2011) found that heavier drinkers reported higher levels of rewarding or stimulant effects, and less sedative effects following an intoxicating dose of alcohol regardless of the BAC limb. The authors concluded that the DM should be simplified by eliminating limb specific alcohol effects, and focusing on effects observed at peak BAC (King et al., 2011). Consistent with the King et al. (2011) study, the results of the current study also suggest that a modification to the DM is necessary. Contrary to King et al. (2011), however, it was found that limb specific SR is important. Rather than a single measure of SR on the ascending limb, descending limb,

or peak BAC, it is suggested that change in SR may be most informative in predicting future drinking behavior. Individuals who maintain greater stimulant effects following alcohol consumption appear to receive greater positive reinforcement to continue drinking. Continued drinking is further reinforced by a faster elimination of sedative effects. This finding highlights the importance of measuring subjective response at multiple time points, across both the ascending and descending limb of the BAC curve as changes in SR may be more informative in predicting drinking behavior than a single, limb specific measurement.

CLINICAL IMPLICATIONS

The current study provides support for a relation between alcohol metabolism and subjective response to alcohol, and how individual differences in alcohol pharmacokinetics may influence drinking behavior through changes in subjective response. The results of the current study have considerable implications for prevention and treatment programs, including behavioral and pharmacological interventions.

Although SR to alcohol has been identified as a risk factor for alcohol problems for some time, SR is rarely discussed in traditional treatment approaches for alcohol use disorders (Schuckit, Kalmijn, Smith, Saunders, & Fromme, 2012). Interventions designed to modify alcohol expectancies, or beliefs about effects of alcohol, are more common and have shown some success in reducing drinking, especially among young males (Labbe & Maisto, 2011). Indeed, alcohol expectancy challenges have been identified as a recommended treatment strategy for reducing alcohol use among college students by the National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2005), one of only three treatment approaches that have shown evidence of effectiveness among

college students. While alcohol expectancy challenge approaches have been shown to be effective in modifying preexisting expectancies (Corbin et al., 2001; Weirs & Kummeling, 2004; Weirs et al., 2005), results of studies testing the effectiveness of alcohol challenge paradigms at reducing alcohol consumption have been equivocal (Corbin, McNair, & Carter, 2001; Jones, Silvia, & Richman, 1995; Weirs & Kummeling, 2004; Weirs, van de Luitgaarden, van den Wildenberg, & Smulders, 2005). Expectancy challenge and other behavioral interventions may benefit from the finding that greater acute tolerance to sedative effects is associated with increased alcohol consumption. For many college student drinkers, experiencing a more rapid reduction in the sedative properties of alcohol is likely viewed as a positive attribute. While experiencing less sedation may be desirable, the attenuated response also poses significant risk by encouraging continued consumption. Previous research has documented a more rapid recovery in subjective intoxication relative to alcohol-induced disinhibition or behavioral control (Weafer & Fillmore, 2012). Feeling more alert may also lead the individual to assume that they are less intoxicated than they actually are and increase the likelihood of engaging in destructive behaviors such as driving an automobile. Education programs aimed at reducing drinking and related consequences on college campuses would benefit by incorporating information about the impact of acute tolerance on drinking behaviors, and modifying normative beliefs and expectancies related to tolerance. Student drinkers might be encouraged to focus more on the amount consumed rather than how intoxicated they feel when making decisions about drinking or driving after drinking.

Although numerous pharmacological interventions have been approved by the Food and Drug Administration for the treatment of alcohol dependence, those with the

most promise have been shown to reduce the reinforcing properties (e.g., subjective stimulation) and cue induced craving for the drug (Anton, Drobes, Voronin, Durazo-Avizu, & Moak, 2004; Anton et al., 2012; Drobes, Anton, Thomas, & Voronin, 2004). One such medication, naltrexone, has received considerable empirical attention and is widely used for the treatment of alcohol dependence. It has been proposed that the stimulant response to alcohol observed in heavy drinkers is the result of increased dopamine release (King et al., 2002; Ray et al., 2010; Thomas et al., 2004), and naltrexone minimizes alcohol induced stimulation by reducing ventral striatal dopamine output (Anton et al., 2004; Gonzales & Weiss, 1998; Ray & Hutchison, 2007). The effect of naltrexone as a treatment for alcohol dependence is moderate at best, and there is considerable need for the identification of factors that may indicate who would benefit most from naltrexone treatment. Recent research into the pharmacogenetics of alcohol and naltrexone indicated that individuals with specific genetic polymorphisms on the mu opioid gene (OPRM1 asn40asp) and dopamine transporter gene (DAT VNTR 9) reported the highest levels of subjective stimulation and consumed the least amount of alcohol while on naltrexone (Anton et al., 2012). It has been suggested that this OPRM1 genetic polymorphism mediates the effects of naltrexone treatment, by causing a greater reduction in the stimulant effects of alcohol while on the medication relative to those without the candidate gene (Anton et al., 2008; Ray & Hutchison, 2007). The current study adds to the growing literature on pharmacological processes that impact stimulant alcohol effects by establishing a link between rate of metabolism and subjective stimulation. Although speculative, rate of metabolism may be a biomarker of stimulant alcohol response, and a potential indicator of naltrexone treatment response.

LIMITATIONS

Several limitations were present in the current study and should be considered when interpreting of the results. First, the sample consisted primarily of Caucasian college students and may not be generalizable to other populations, including older adults, those from different ethnic groups, and individuals who did not attend college. Additionally, the study excluded those with diagnosable alcohol use disorders as well as individuals with minimal experience with alcohol. It may be that the pattern of response that confers risk for alcohol problems changes with drinking experience. Furthermore, developmental changes in pharmacokinetics may occur (Kelly, Bonthius & West, 1987), and variations in metabolism that occur with prolonged exposure to alcohol may have influenced the relations between alcohol pharmacokinetics and subjective response in the current study. Additional studies that utilize longitudinal designs to track changes in subjective response over time are necessary to test these hypotheses. Future studies that utilize larger samples of individuals with a family history of alcoholism would be also be advantageous as previous research has indicated that those with a positive family history of alcoholism differ in their subjective response to alcohol from those without a family history of the disorder.

When examining objective and subjective response to alcohol it is beneficial to obtain measurements in settings that are consistent with typical drinking environments, as response to alcohol has been shown to vary according to the drinking environment (Corbin, Scott, & Boyd, under review). The current study is strengthened by the use of a simulated bar and group drinking context that is more consistent with an environment in

which college drinking typically occurs. Nonetheless, results of the current study may not generalize to other drinking contexts, such as drinking alone or to social drinking in non-bar settings (e.g., house party). Moreover, despite the very realistic nature of the simulated bar laboratory used in this study, it is not truly a natural drinking context, and participants were drinking with individuals with whom they were unfamiliar. Different SR profiles may confer risk in other settings that differ in both physical features and social dynamics.

The lack of a placebo control condition in the current study may also be viewed as a limitation. Although SR to alcohol is an interpretation of the pharmacological effects of alcohol, it is also influenced by expectancies, or beliefs about the effects of the drug. When examining SR to alcohol, it is often necessary to tease apart pharmacology from expectancy (Fromme, D'Amico, & Katz, 1999; Jones, Corbin, & Fromme, 2001; Zhang, Welte, & Wieczorek, 2002). Towards this end, researchers commonly utilize placebos in experimental designs to separate pharmacology from expectancy or to control for the influence of expectancy. The decision to omit a placebo condition from the current study was deliberate, as the primary aim was to assess the impact of pharmacokinetic processes on SR, which would not be present in a placebo condition. Nonetheless, results of the current study regarding relations between subjective response and ad-lib consumption must be interpreted with caution, as an expectancy basis for these associations cannot be ruled out.

The dosing procedures in this study may have also contributed to the largely null findings regarding relations between rate of absorption and SR. Although the drinking pace was less rapid than in many prior alcohol administration studies, the rate of

consumption was likely more rapid than is typical in social bar settings. This relatively rapid pace of administration may have contributed to reduced variability in alcohol absorption, thereby limiting the ability to detect relations with SR. As in most other alcohol administration studies, considerable efforts were made to minimize environmental factors known to influence the pharmacokinetics of alcohol. Accordingly, dosing procedures were standardized such that participants consumed the alcohol beverages at a consistent rate (10 minutes per beverage). Future studies that utilize experimental designs to manipulate variables known to impact absorption (e.g., pace of consumption, stomach contents) would provide an important contribution and might allow for the identification of stronger links between rate of absorption and subjective responses.

The study is further limited by the reliance on subjective measures of stimulation, sedation, and craving. Previous research has suggested that alcohol dependent individuals experience an attenuated response to several physiological responses following alcohol consumption, including static ataxia (Schuckit, 1985), cortisol release (Schuckit et al., 1987), and heart rate (Ehlers & Schuckit, 1991). Pharmacokinetic processes, such as rate of metabolism, may well relate to response to these objective physiological measures, which may further mediate the relation between metabolism and drinking behavior. Objective measures of alcohol craving following cue reactivity paradigms are also widely used and may be a more accurate indicator of desire to consume alcohol than subjective reports of craving (Monti et al., 2000; Schacht, Anton, & Myrick, 2013). The largely null findings regarding the relations of craving with SR

and pharmacokinetics may have been due to the self-reported craving measure used and/or the desire to respond in a socially appropriate manner in a group setting.

As noted previously, the primary outcome variable, ad-lib consumption, was assessed towards the end of the study protocol. The proximity of the taste rating task to the descending limb measures may explain many of the null findings between rate of absorption, ascending limb measures of SR, and ad-lib consumption. Including a similar ad-lib consumption period during the ascending limb of the blood alcohol curve may produce different results. The short duration of the ascending limb of the BAC curve would likely make this difficult in traditional alcohol administration research. However, as indicated earlier, slower dosing procedures might allow for greater variability in rates of absorption while also providing an opportunity to examine ad-lib consumption as blood alcohol levels are rising.

A final limitation involves the use of non-alcoholic beer during the ad-lib consumption period, as participants may have assumed that no alcohol was present and limited their intake. It is worth noting, however, that only one participant speculated that the beverage was non-alcoholic. The amount consumed during the taste rating task for this single participant was treated as missing in the analyses. Moreover, the mean level consumed during the taste-rating task was nearly 1 full beer (320 ml), suggesting that participants largely perceived that they were alcoholic beers.

FUTURE DIRECTIONS

As noted previously, several genetic polymorphisms have been identified as biomarkers of subjective response to alcohol, including OPRM1 for stimulation and $GABA_A$ for sedation (Anton et al., 2012; Fromme et al., 2004; Ray & Hutchison, 2004).

While these results are highly informative in identifying those most likely to benefit from pharmacological treatment, genetic testing is often unavailable to those seeking treatment for alcohol dependence. Other biomarkers of an individual's potential response to pharmacological treatment may be more easily obtained by treatment staff, without the use of costly and time intensive methods. One such method may be assessing variability in alcohol pharmacokinetics. Results of the current study suggest that those who metabolize alcohol more quickly report greater subjective stimulation and experience a greater reduction in the sedative effects of alcohol, and indicate that a faster metabolism may confer greater risk for alcohol related problems by facilitating increased consumption. Variability in pharmacokinetics may relate to the pharmacodynamic processes that have been shown to influence subjective response to alcohol and response to naltrexone treatment (e.g., OPRM1). If this is the case, pharmacokinetic variability may be an important risk factor for the development of alcohol use disorders and provide an easily measureable biomarker for inferring successful treatment outcomes with naltrexone. Future studies examining relations between pharmacokinetic processes and these identified genetic polymorphisms prior to and following naltrexone treatment are necessary to address this hypothesis.

The results of the current study suggest that those who are most at risk for heavy alcohol consumption experience greater acute sensitization to stimulant effects and greater acute tolerance to sedative effects as blood alcohol levels decline. In other words, at risk individuals experience both positive and negative reinforcement to continue drinking by maintaining more of the desirable stimulant effects of alcohol while simultaneously diminishing aversive stimulant effects. This high risk profile appears to

be driven, in part, by a more rapid metabolism. While the temporal ordering of the measures used in the current study provides greater confidence in the direction of effects, it is impossible to ascertain whether the relations of metabolism and SR with drinking behavior would be consistent over time and in other drinking contexts. Future studies may find that alcohol metabolism becomes more efficient with increased exposure to alcohol and during the progression from use to dependence. These changes in metabolism may further exaggerate the identified risk profile of stimulant maintenance and sedative tolerance that may help sustain problematic use and interfere with treatment outcome.

Previous prospective studies that have examined subjective response to alcohol have been limited in that they have focused primarily on the examination of sedative alcohol effects assessed on the descending limb of the blood alcohol curve (Morean & Corbin, 2010; Quinn & Fromme, 2011). These studies have typically found that those with a family history of alcoholism and those with alcohol dependence report an attenuated response to descending limb sedative effects (Schuckit, Smith, Anderson, & Brown, 2004). The results of the current study suggest that the results of these longitudinal studies may be misleading, as those with a greater acute tolerance to sedation were most likely to consume more within session. Results such as these highlight the importance of assessing change in subjective response over time during the drinking session. Furthermore, the current study found that a greater response to stimulant effects on the descending limb was predictive of greater within session consumption, which stresses the importance of assessing the full range of alcohol effects on both the ascending and descending limb of the blood alcohol curve.

CONCLUSION

The current study provides additional support for SR as an endophenotype of problematic alcohol use and risk for alcohol use disorders. Variability in alcohol metabolism was found to influence the SR experienced, thus providing a biological attribution to SR. Individuals who metabolized alcohol more quickly reported higher overall levels of stimulation, greater retention of stimulant effects from the ascending to descending limb, and a more rapid reduction in sedative effects. Individual differences in alcohol metabolism were found to have an indirect influence on drinking behavior. The profile of SR evident among participants with faster metabolism subsequently led to greater within-session alcohol consumption, and suggests that rate of metabolism may indicate an easily identifiable biomarker for acute alcohol problems.

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Table 1

Summary of Variables Included in Each Model

	Model Number								
Variable Name	1	2	3	4	5	6	7	8	9
Absorption Rate	X	X	X				X	X	X
Metabolism Rate				X	X	X	X	X	X
Asc. Stimulation	X	X	X				X	X	X
Asc. Sedation	X	X	X				X	X	X
Asc. Craving	X		X				X		X
Desc. Stimulation				X	X	X	X	X	X
Desc. Sedation				X	X	X	X	X	X
Desc. Craving				X		X	X		X
Ad-lib Consumption		X	X		X	X		X	X

Table 2

Descriptive Statistics of Drinking History Variables

Variable	M	SD	Range	Skewness	Kurtosis
Age	22.3	1.75	9.00	2.38	6.94
Drinking Frequency†	8.43	4.98	26.00	1.33	3.00
Total Monthly Consumption†	40.29	31.82	149.00	1.41	1.85
Binge Drinking†	3.90	3.51	15.00	1.09	.528
Alcohol Consequences††	18.82	9.21	42.00	.243	-.339

Note. N = 98; †Consumed during the past 30 days; ††Total number of consequences due to alcohol use during the past year from Young Adult Alcohol Consequences Questionnaire.

Table 3

Frequency Distributions for Background Characteristics

Variable	N
Gender	
Male	67
Female	31
Total family income for past year	
Under $16,000	10
$16,000 – $39,999	12
$40,000 – $69,999	16
$70,000 – $99,999	14
$100,000 – $299,999	39
$300,000 or more	7
Racial Identity	
American Indian/Alaskan Native	3
Asian	5
Black or African American	3
White/Caucasian	77
Other	8
Ethnic Identity[†]	
Hispanic/Latino	15
Non-Hispanic/Latino	81
Highest Level of Education Completed	
High School Diploma or Equivalent (GED)	4
In College, but have not received a degree	71
Associates Degree	14
Bachelor's Degree	8
Master's Degree	1
Nicotine Dependence	
Non-Smoker	82
Low Dependence	3
Low to Moderate Dependence	13
Family History of Alcohol Problems	
Yes	36
No	62

Note. [†]Two participants did not report ethnic identity.

Table 4

Descriptive Statistics of Predictor and Outcome Variables

Variable	M	SD	Range	Skewness	Kurtosis
Ascending Limb AUC	3.56	1.43	5.97	-.02	-.79
Descending Limb AUC	8.83	2.61	12.00	.09	-.41
Asc. Limb Stimulation	5.54	1.97	10.00	-.70	.80
Asc. Limb Sedation	2.16	1.50	8.00	1.10	1.64
Asc. Limb Craving	3.36	1.19	5.00	.35	-.53
Desc. Limb Stimulation	4.61	1.96	8.57	-.24	-.27
Desc. Limb Sedation	2.25	1.78	6.57	.83	-.30
Desc. Limb Craving	2.84	1.13	4.38	.36	-.65
Ad-lib Consumption	319.74	214.50	703.00	.34	-.99

Note. †Total amount consumed in milliliters during taste rating task (maximum = 710 mL).

Table 5

Descriptive Statistics for Pharmacokinetic Parameters

Variable	M	SD	Range	Skewness	Kurtosis
Peak BAC (g%)	.087	.013	.060	.126	-.175
Time to Peak BAC (min.)†	63.16	20.29	80.00	.049	-.493
Total AUC	12.39	3.16	16.17	.451	-.175
BAC at Ascending Limb Assessment (g%)	.074	.013	.058	.754	.129
BAC at Descending Limb Assessment (g%)	.071	.011	.055	.753	.442
Time between Ascending and Descending Limb Assessments (min.)	73.57	33.13	150.00	.709	.108

Note. †Time from beginning of first drink to peak BAC.

Table 6

Correlations between Potential Covariates and Variables of Primary Interest

	Sex	Age	Race	Family History†	Drinks/Day††	Nicotine Dependence
Ascending AUC	-.068	-.082	.196	-.111	.076	-.044
Descending AUC	-.320**	.165	-.130	.084	-.073	-.086
Asc. Stimulation	.056	-.131	.098	.051	.088	.083
Asc. Sedation	.146	.032	-.019	.123	-.106	.299**
Asc. Craving	-.093	.024	.079	.149	-.051	.057
Desc. Stimulation	.099	-.177	.026	.120	.001	.032
Desc. Sedation	-.019	.133	-.096	-.198*	-.139	.275**
Desc. Craving	-.128	-.025	.153	.002	-.037	-.110
Ad-lib Consumption	-.337**	-.182	.193	-.026	.334**	-.010

Note. *$p < .05$; **$p < .01$; †One or more parent described as a probable or definite problem drinker; ††Typical number of drinks consumed per drinking day.

Table 7

Correlations between Predictor and Outcome Variables

	1	2	3	4	5	6	7	8	9
1. Ascending AUC	--	.150	.004	-.050	-.037	-.042	.049	.030	.072
2. Descending AUC		--	-.081	-.069	.072	-.231*	.097	-.021	-.056
3. Asc. Stimulation			--	.038	.181	.696**	.159	.048	.091
4. Asc. Sedation				--	.077	.175	.658**	-.045	-.045
5. Asc. Craving					--	.187	.152	.660**	.166
6. Desc. Stimulation						--	.164	.149	.184
7. Desc. Sedation							--	.029	-.119
8. Desc. Craving								--	.304**
9. Ad-lib Consumption									--

Note. $^{*}p < .05$; $^{**}p < .01$

Table 8

Specific Indirect Effects and Standard Errors for Model 1

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3$	$\gamma_{11}\beta_{31}$	.001	.027	-.050	.052
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3$	$\gamma_{21}\beta_{32}$	-.002	.014	-.030	.025

Note. ξ_1 = Ascending limb AUC; η_1 = Ascending Stimulation; η_2 = Ascending Sedation; η_3 = Ascending Craving.

Table 9

Specific Indirect Effects and Standard Errors for Model 2

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3$	$\gamma_{11}\beta_{31}$	.000	.014	-.026	.027
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3$	$\gamma_{21}\beta_{32}$	-.001	.011	-.023	.020

Note. ξ_1 = Ascending limb AUC; η_1 = Ascending Stimulation; η_2 = Ascending Sedation; η_3 = Ad-lib Consumption.

Table 10

Specific Indirect Effects and Standard Errors for Model 3

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_4$	$\gamma_{11}\beta_{41}$	.000	.012	-.024	.025
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_4$	$\gamma_{21}\beta_{42}$	-.001	.012	-.024	.022
$\xi_1 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{31}\beta_{43}$	-.002	.018	-.036	.033
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{11}\beta_{31}\beta_{43}$	.000	.005	-.009	.009
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{21}\beta_{32}\beta_{43}$	.000	.003	-.006	.005

ξ_1 = Ascending limb AUC; η_1 = Ascending Stimulation; η_2 = Ascending Sedation; η_3 = Ascending Craving; η_4 = Ad-lib Consumption.

Table 11

Specific Indirect Effects and Standard Errors for Model 4

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3$	$\gamma_{11}\beta_{31}$	-.037	.036	-.107	.033
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3$	$\gamma_{21}\beta_{32}$	.001	.018	-.033	.036

Note. ξ_1 = Descending limb AUC; η_1 = Descending Stimulation; η_2 = Descending Sedation; η_3 = Descending Craving.

Table 12

Specific Indirect Effects and Standard Errors for Model 5

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3$	$\gamma_{11}\beta_{31}$	-.059	.038	-.134	.016
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3$	$\gamma_{21}\beta_{32}$	-.012	.018	-.048	.024

Note. ξ_1 = Descending limb AUC; η_1 = Descending Stimulation; η_2 = Descending Sedation; η_3 = Ad-lib Consumption.

Table 13

Specific Indirect Effects and Standard Errors for Model 6

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_4$	$\gamma_{11}\beta_{41}$	-.046	.035	-.115	.023
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_4$	$\gamma_{21}\beta_{42}$	-.012	.018	-.047	.023
$\xi_1 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{31}\beta_{43}$	-.008	.031	-.069	.052
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{11}\beta_{31}\beta_{43}$	-.010	.010	-.030	.010
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{21}\beta_{32}\beta_{43}$	.000	.005	-.010	.011

ξ_1 = Descending limb AUC; η_1 = Descending Stimulation; η_2 = Descending Sedation; η_3 = Descending Craving; η_4 = Ad-lib Consumption.

Table 14

Specific Indirect Effects and Standard Errors for Model 7

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3$	$\gamma_{11}\beta_{31}$	-.003	.020	-.042	.036
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3$	$\gamma_{21}\beta_{32}$	-.008	.016	-.039	.023

Note. ξ_1 = Descending limb AUC; η_1 = Change in Stimulation; η_2 = Change in Sedation; η_3 = Change in Craving.

Table 15

Specific Indirect Effects and Standard Errors for Model 8

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3$ †	$\gamma_{11}\beta_{31}$	-.061	.013	-.129	.006
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3$	$\gamma_{21}\beta_{32}$	-.030	.004	-.077	.016

Note. ξ_1 = Descending limb AUC; η_1 = Change in Stimulation; η_2 = Change in Sedation; η_3 = Ad-lib consumption. †90% CI [-.118, -.004].

Table 16

Specific Indirect Effects and Standard Errors for Model 9

Effect	Parameter	Estimate	Standard Error	95% CI LCL	95% CI UCL
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_4$	$\gamma_{11}\beta_{41}$	-.045	.032	-.107	.017
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_4$	$\gamma_{21}\beta_{42}$	-.035	.025	-.083	.014
$\xi_1 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{31}\beta_{43}$	-.023	.026	-.073	.028
$\xi_1 \rightarrow \eta_1 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{11}\beta_{31}\beta_{43}$	-.001	.005	-.011	.010
$\xi_1 \rightarrow \eta_2 \rightarrow \eta_3 \rightarrow \eta_4$	$\gamma_{21}\beta_{32}\beta_{43}$	-.002	.004	-.010	.005

Note. ξ_1 = Descending limb AUC; η_1 = Change in Stimulation; η_2 = Change in Sedation; η_3 = Change in Craving; η_4 = Ad-lib consumption.

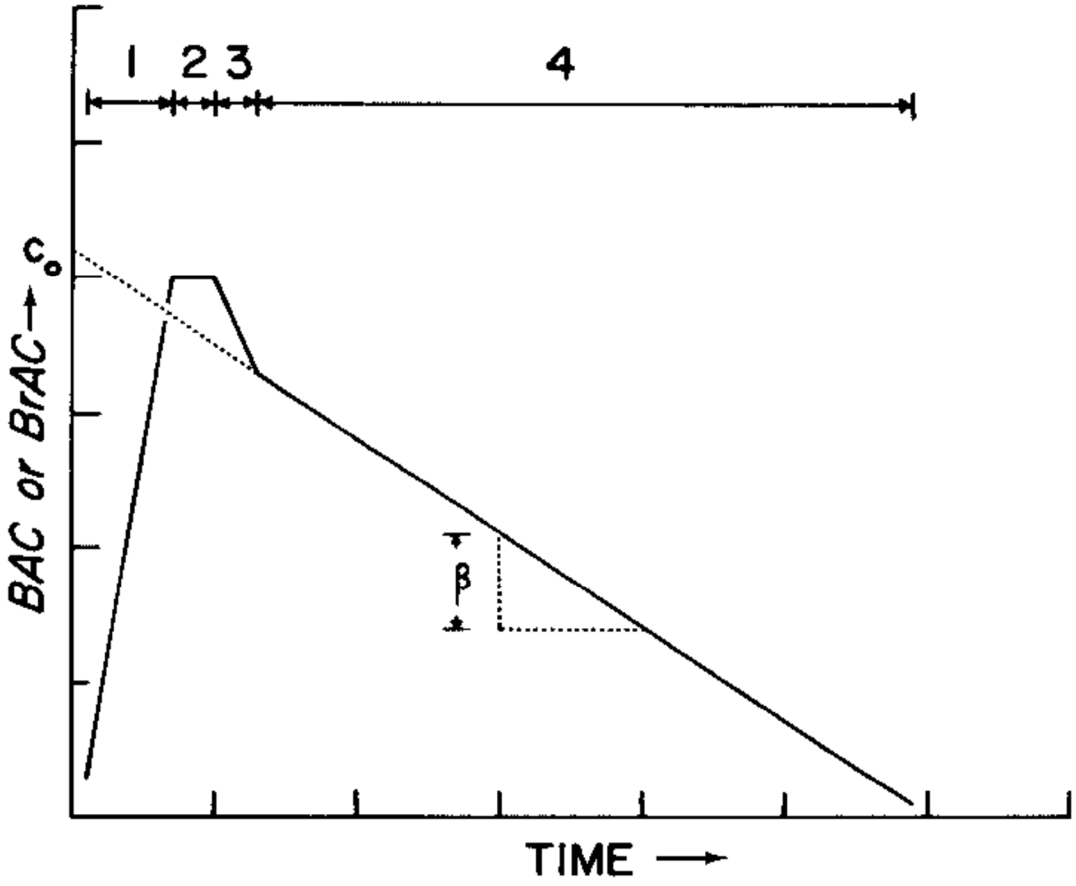

Figure 1. Theoretical blood alcohol concentration curve: 1 = absorption phase; 2 = plateau; 3 = diffusion/equilibration; 4 = elimination phase.

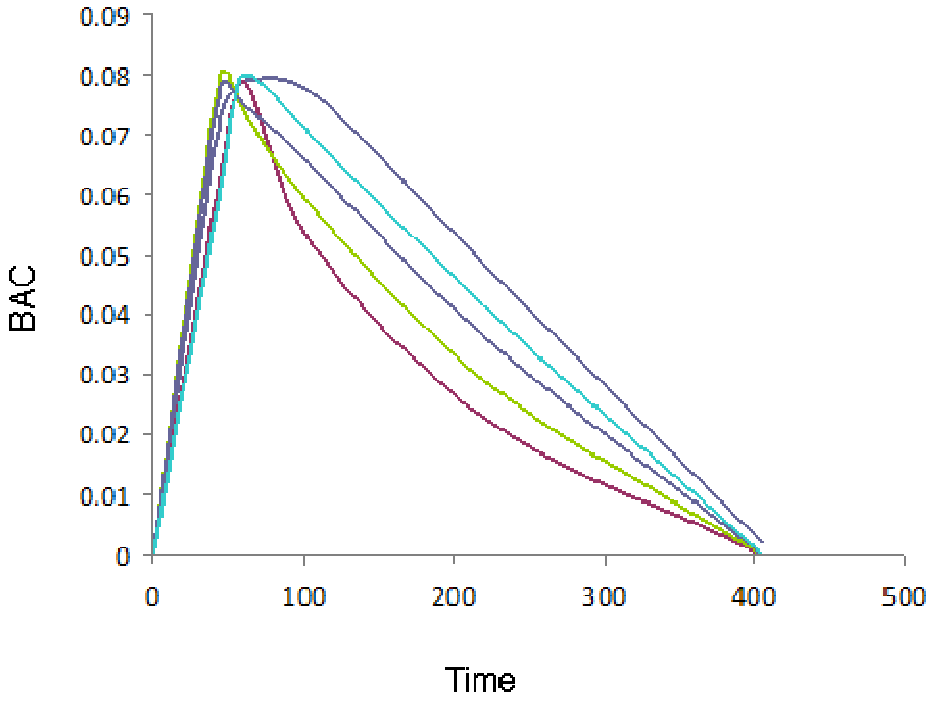

Figure 2. Blood alcohol concentration curves for three individual given an equivalent weight adjusted dose of alcohol during an alcohol administration study.

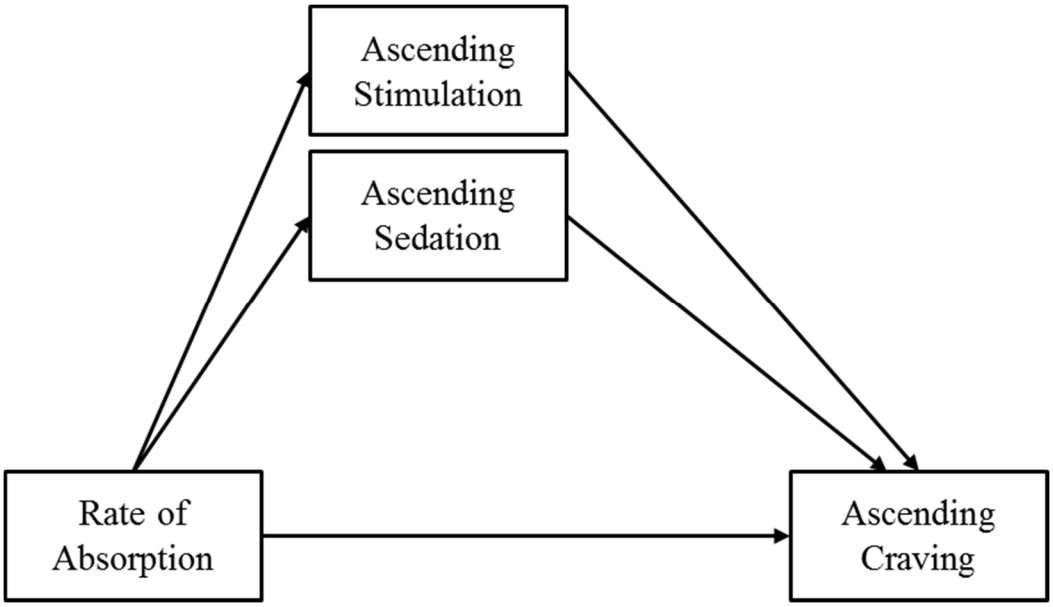

Figure 3. Model 1 assessing relations between rate of absorption and subjective response on craving.

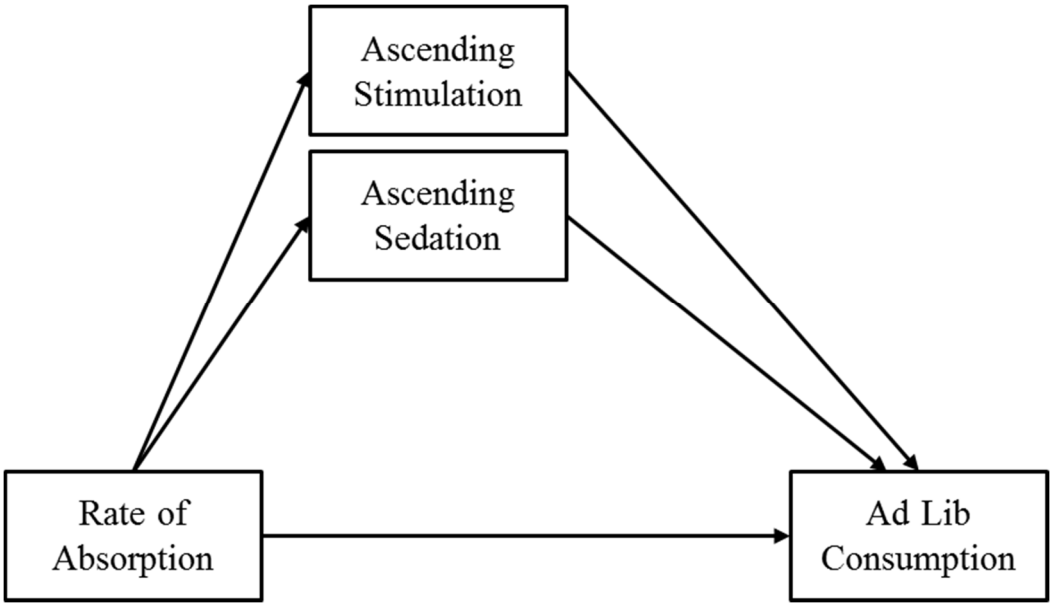

Figure 4. Model 2 assessing relations between rate of absorption and subjective response on ad-lib consumption.

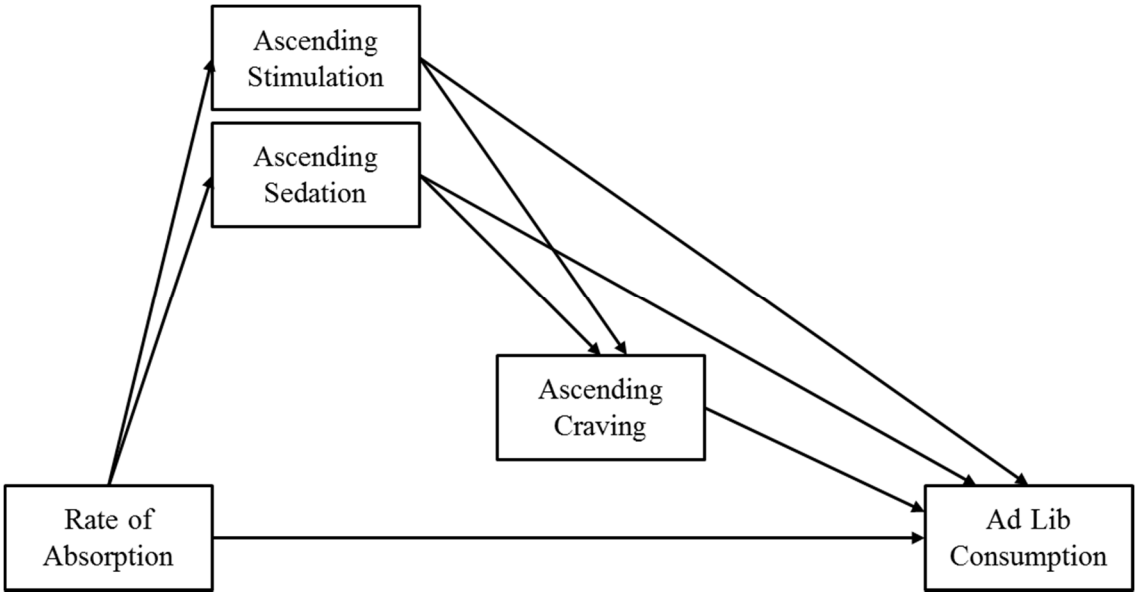

Figure 5. Model 3 assessing relations between rate of absorption and subjective response on craving and ad-lib consumption.

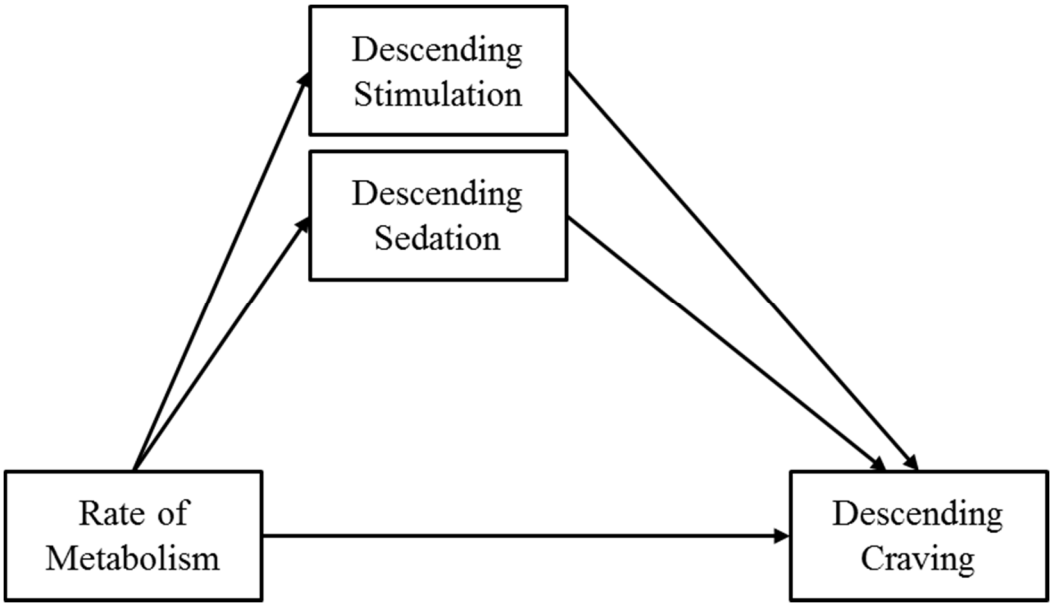

Figure 6. Model 4 assessing relations between rate of metabolism and subjective response on craving.

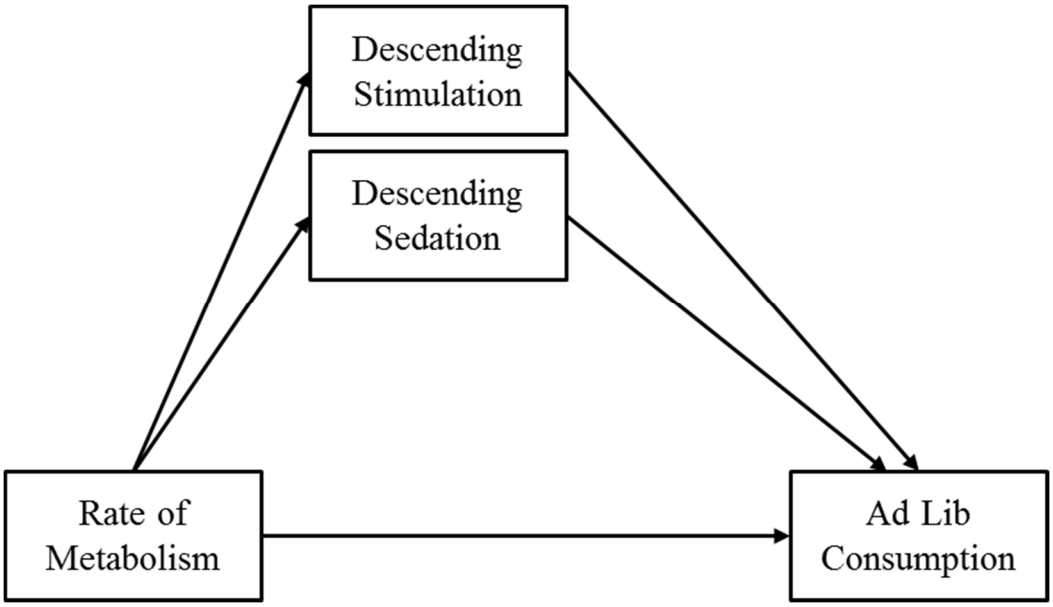

Figure 7. Model 2 assessing relations between rate of metabolism and subjective response on ad-lib consumption.

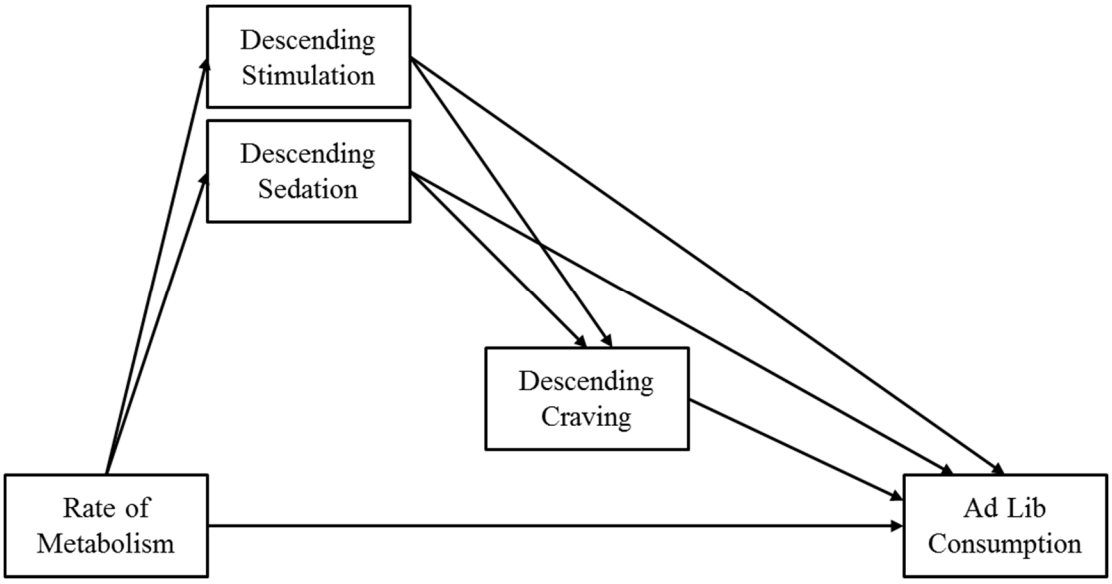

Figure 8. Model 6 assessing relations between rate of metabolism and subjective response on craving and ad-lib consumption.

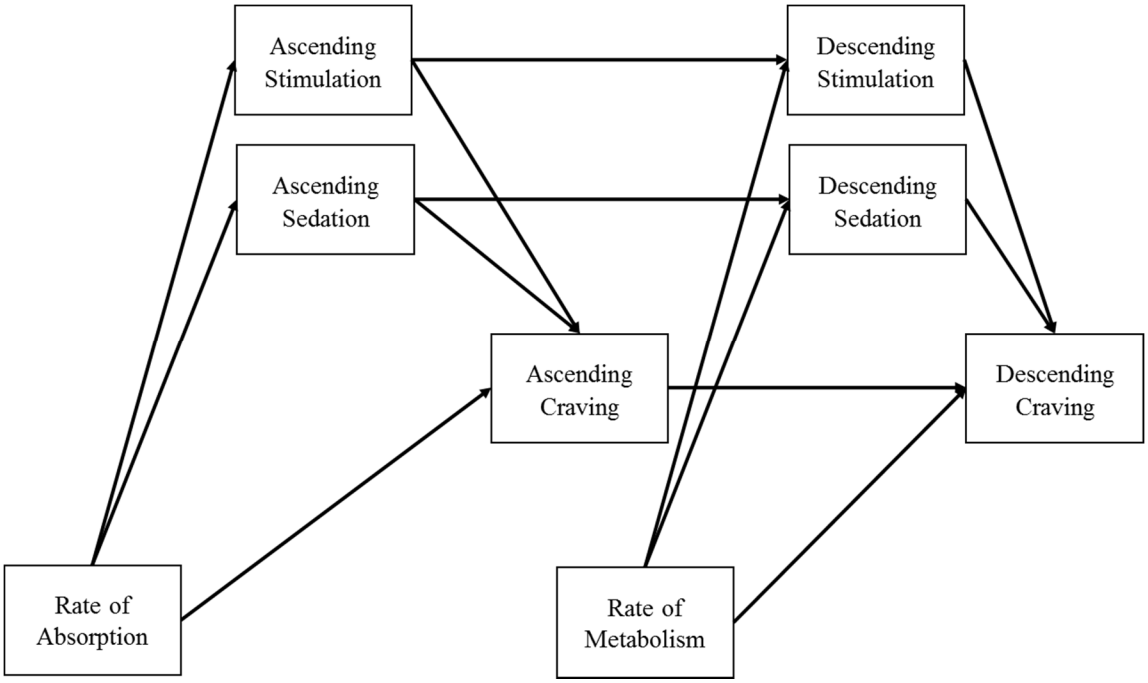

Figure 9. Model 7 assessing relations between ascending and descending limb BAC rate of change and subjective response concurrently on craving.

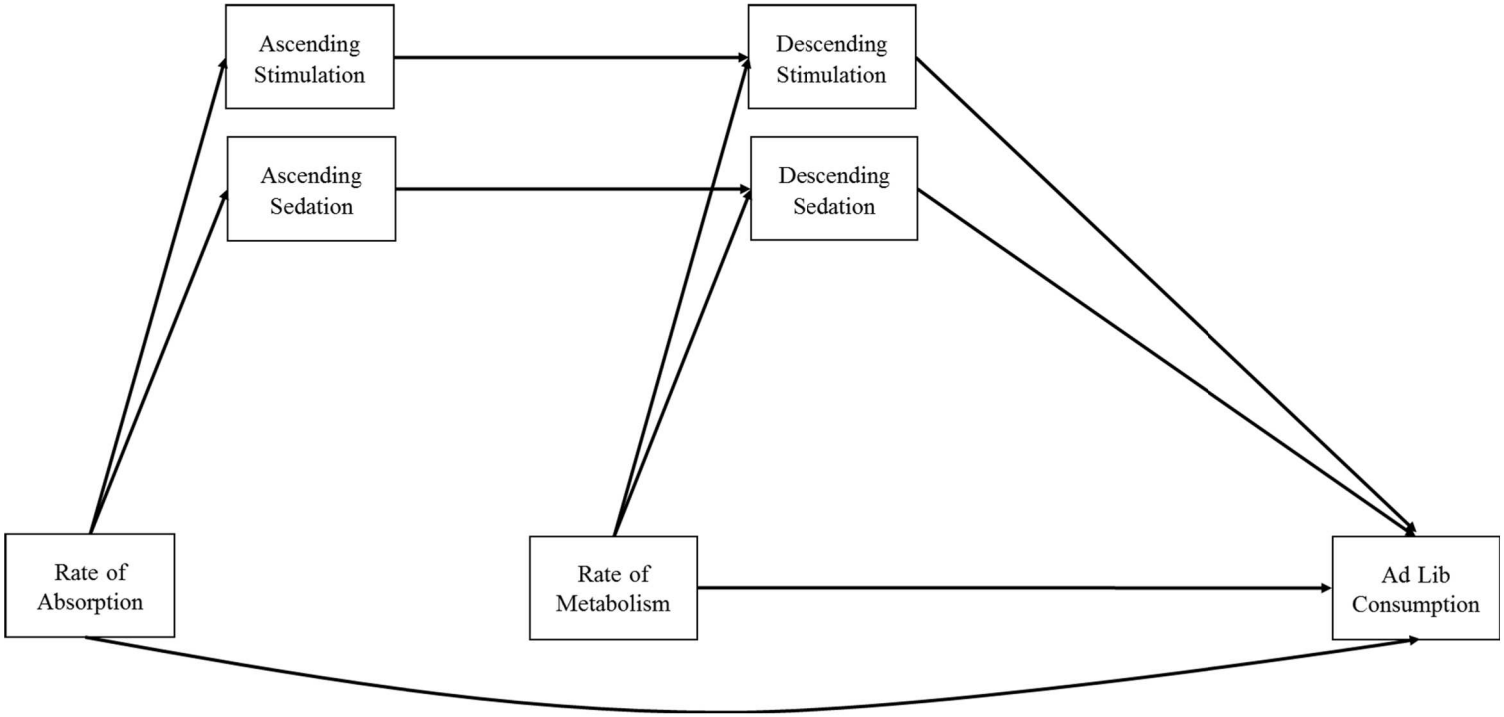

Figure 10. Model 8 assessing relations between ascending and descending limb BAC rate of change and subjective response concurrently on ad-lib consumption.

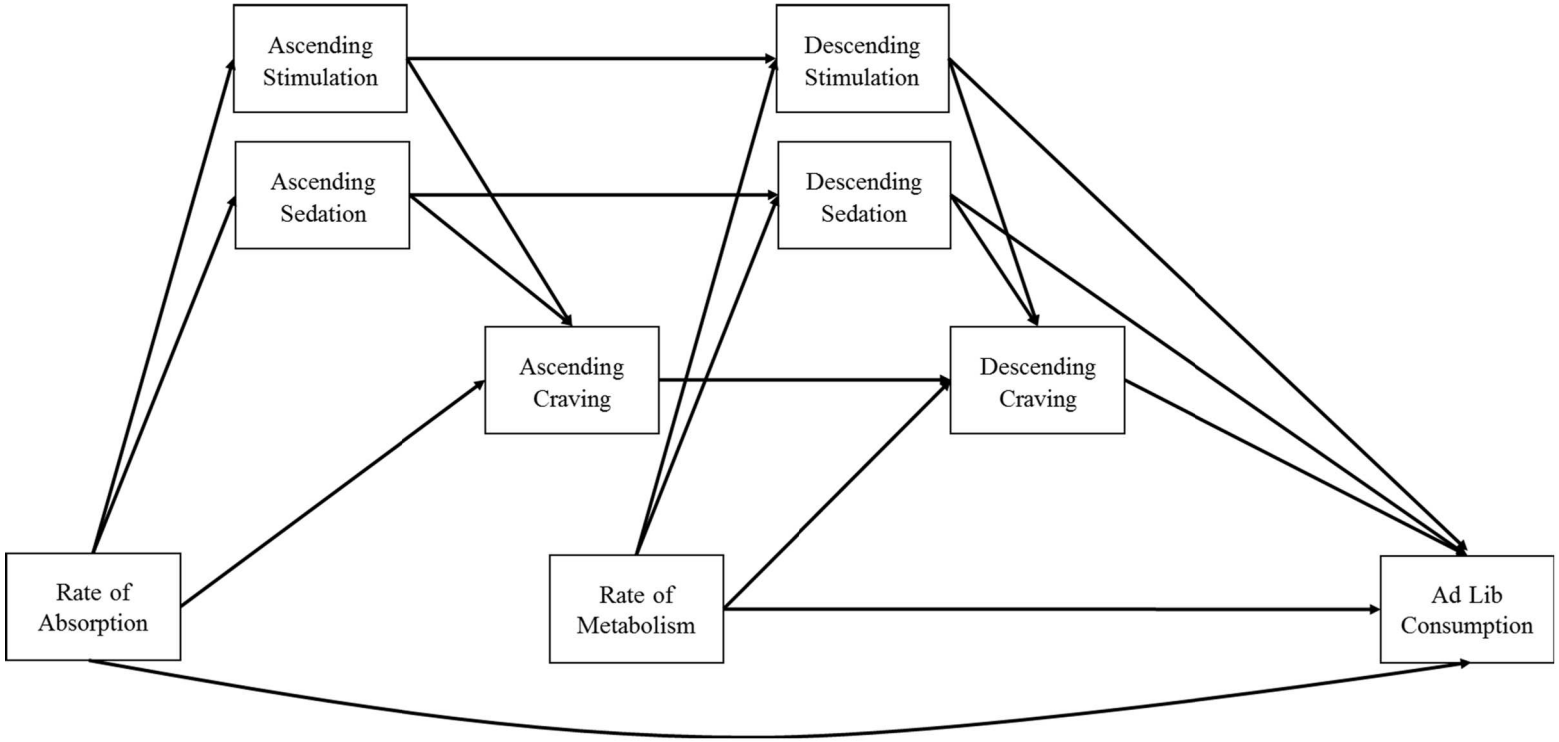

Figure 11. Model 9 assessing relations between ascending and descending limb BAC rate of change and subjective response concurrently on craving and ad-lib consumption.

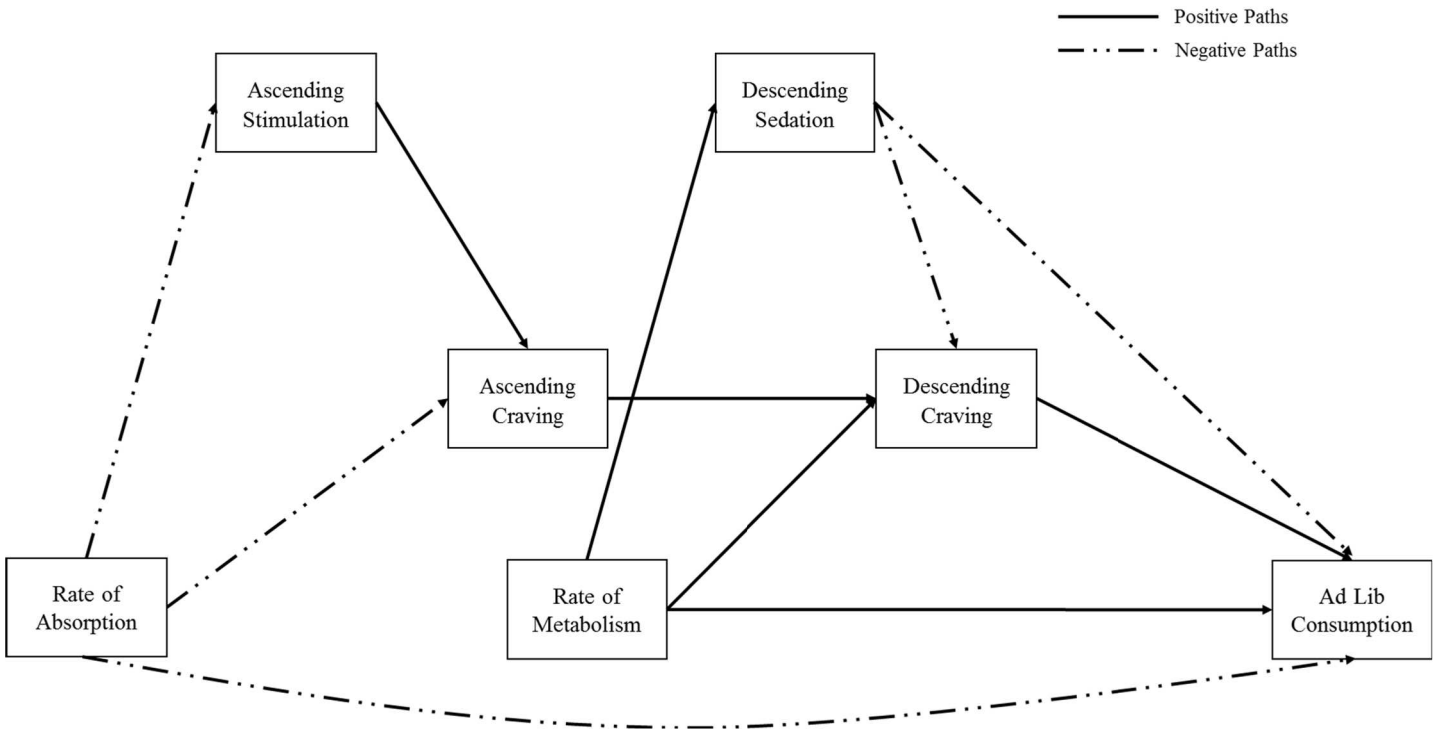

Figure 12. Hypothesized significant paths in Model 9.

Note. Faster rate of absorption is indicated by a smaller area under the curve, slower rate of metabolism is indicated by a larger area under the curve.

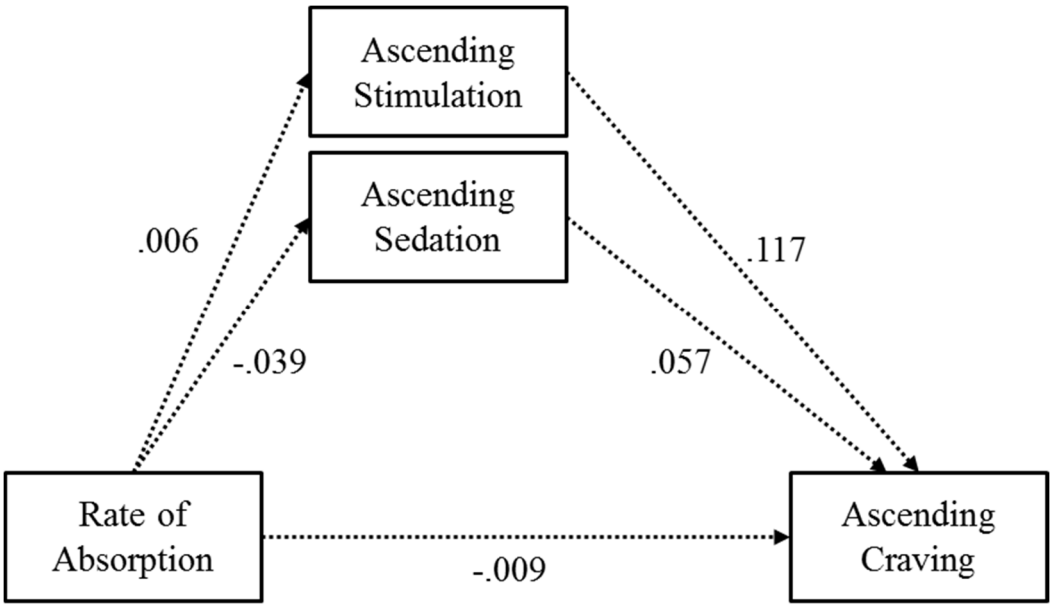

Figure 13. Results of Model 1 showing ascending limb effects on craving.

Note. All values are standardized path coefficients. All paths were not significant ($p >$ .10).

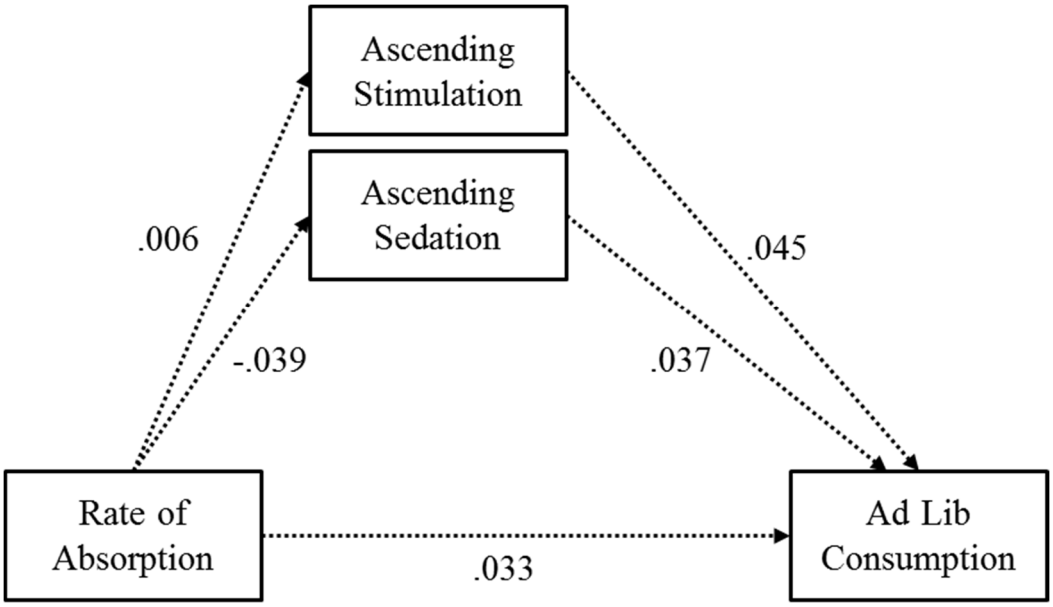

Figure 14. Results of Model 2 showing ascending limb effects on ad-lib consumption.

Note. All values are standardized path coefficients. All paths were not significant ($p >$ .10).

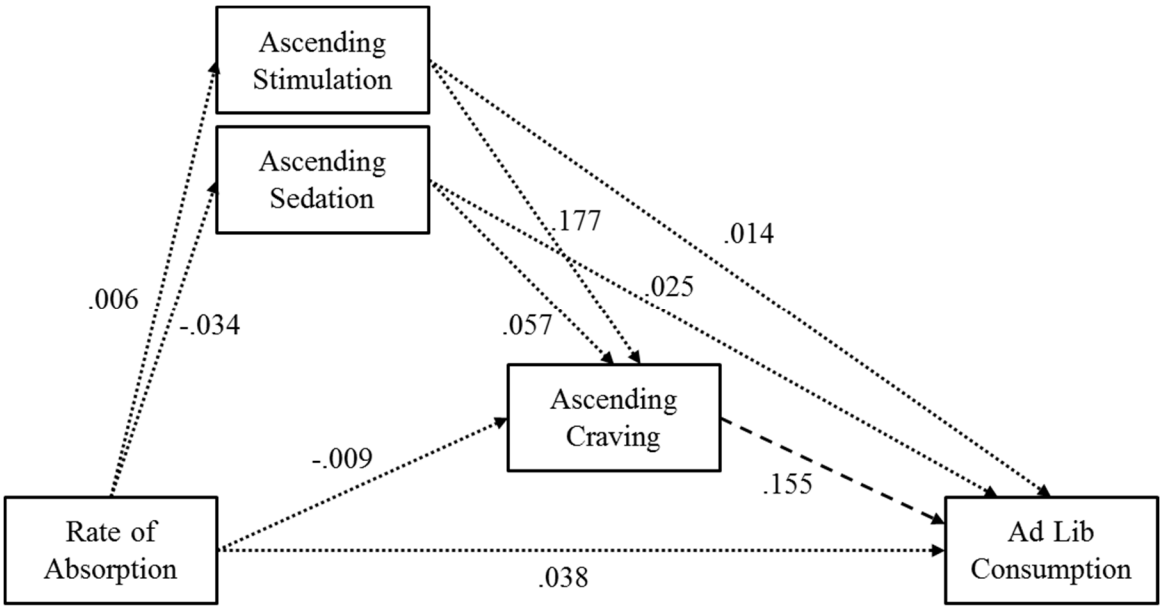

Figure 15. Results of Model 3 showing ascending limb effects on craving and ad-lib consumption.

Note. All values are standardized path coefficients. All paths were not significant ($p >$ .10).

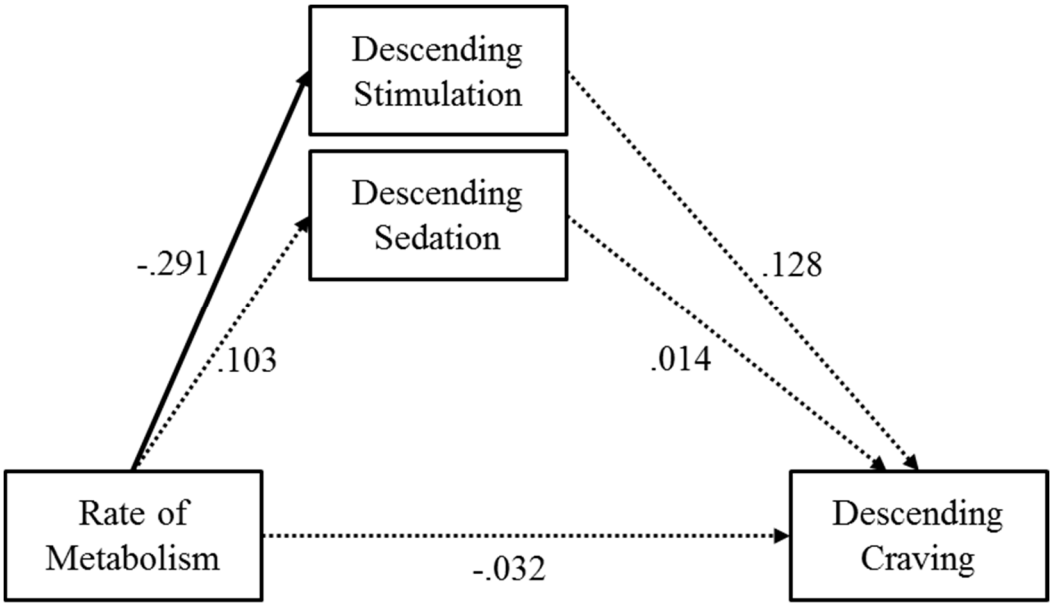

Figure 16. Results of Model 4 showing descending limb effects on craving.

Note. All values are standardized path coefficients. Solid lines indicate significant paths ($p < .05$); dotted lines indicate non-significant paths ($p > .10$).

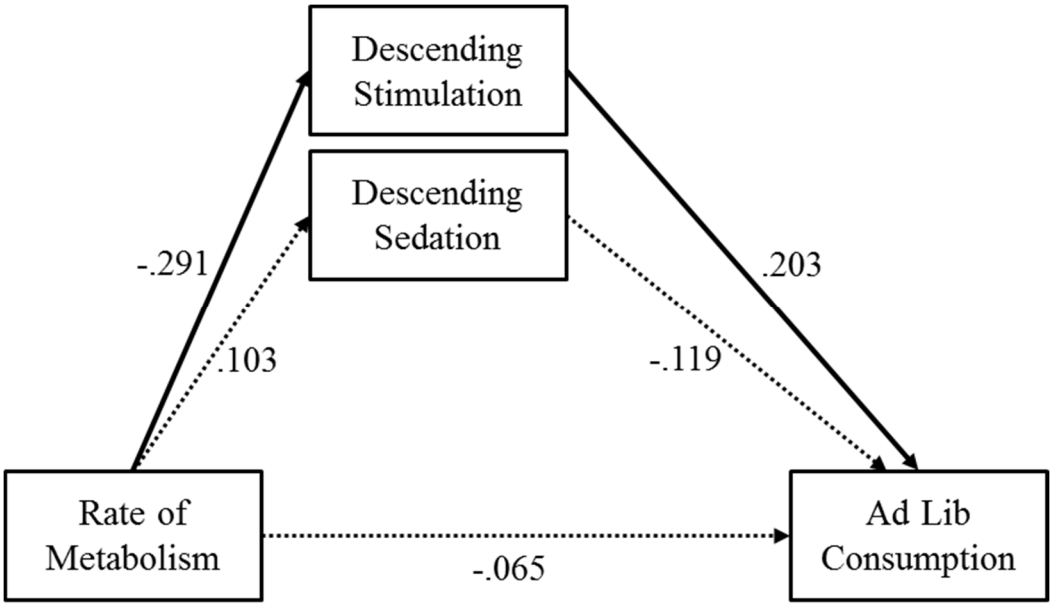

Figure 17. Results of Model 5 showing descending limb effects on ad-lib consumption.

Note. All values are standardized path coefficients. Solid lines indicate significant paths ($p < .05$); dotted lines indicate non-significant paths ($p > .10$).

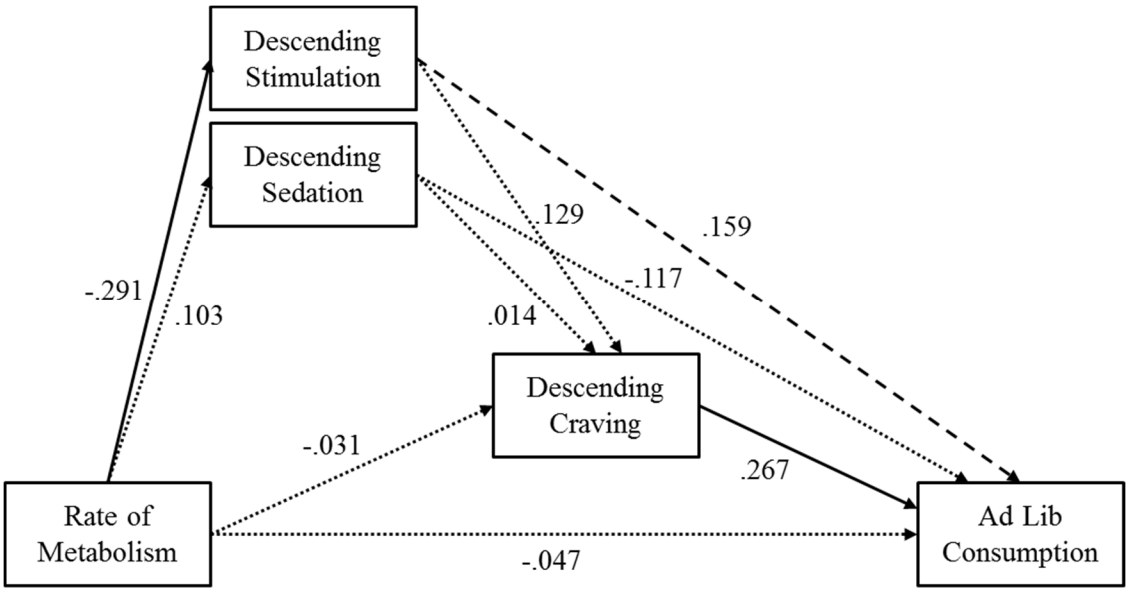

Figure 18. Results of Model 6 showing descending limb effects on craving and ad-lib consumption.

Note. All values are standardized path coefficients. Solid lines indicate significant paths ($p < .05$); dashed lines indicate marginally significant paths ($p < .10$); dotted lines indicate non-significant paths ($p > .10$).

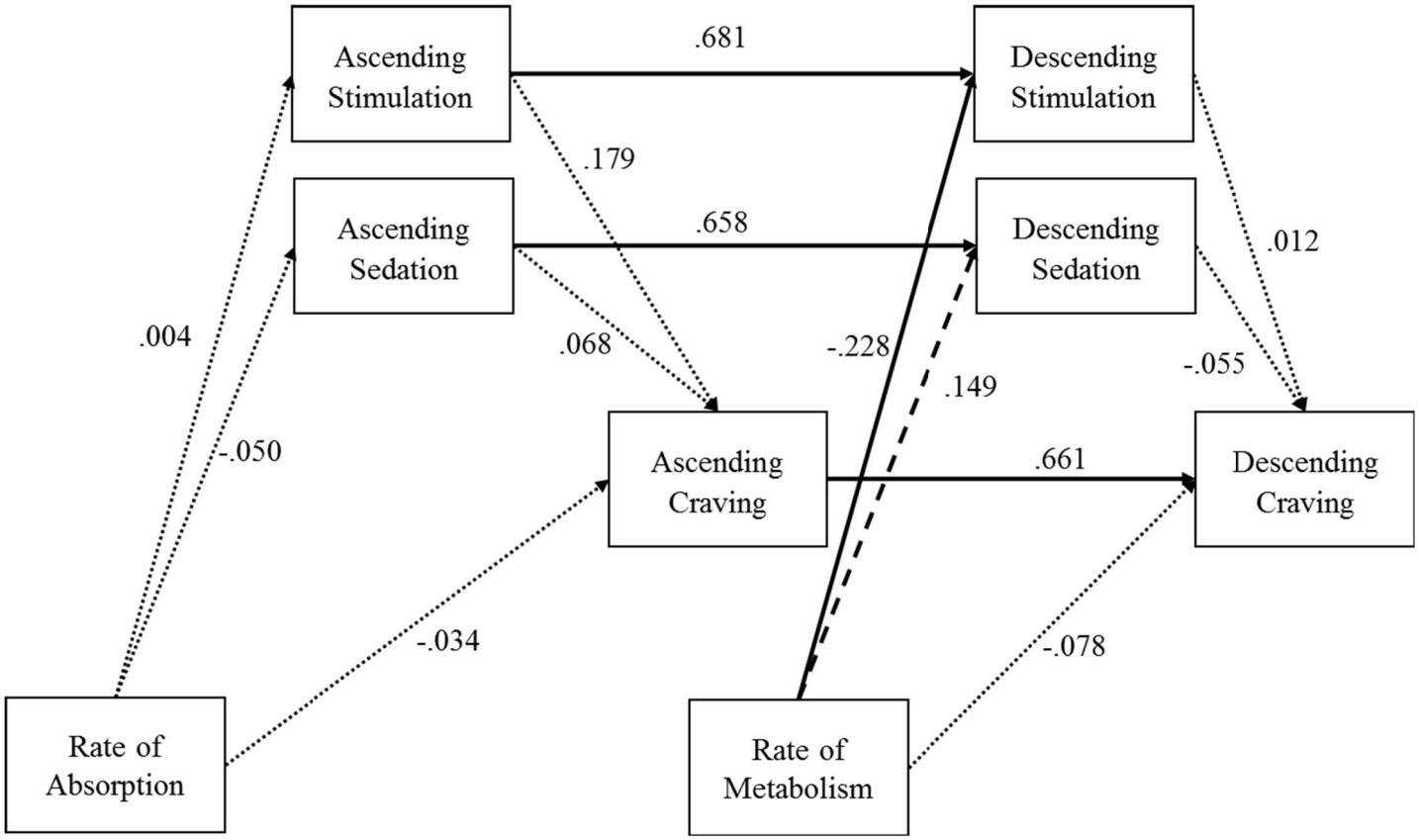

Figure 19. Results of Model 7 showing ascending and descending limb effects on craving.

Note. All values are standardized path coefficients. Solid lines indicate significant paths ($p < .05$); dashed lines indicate marginally significant paths ($p < .10$); dotted lines indicate non-significant paths ($p > .10$).

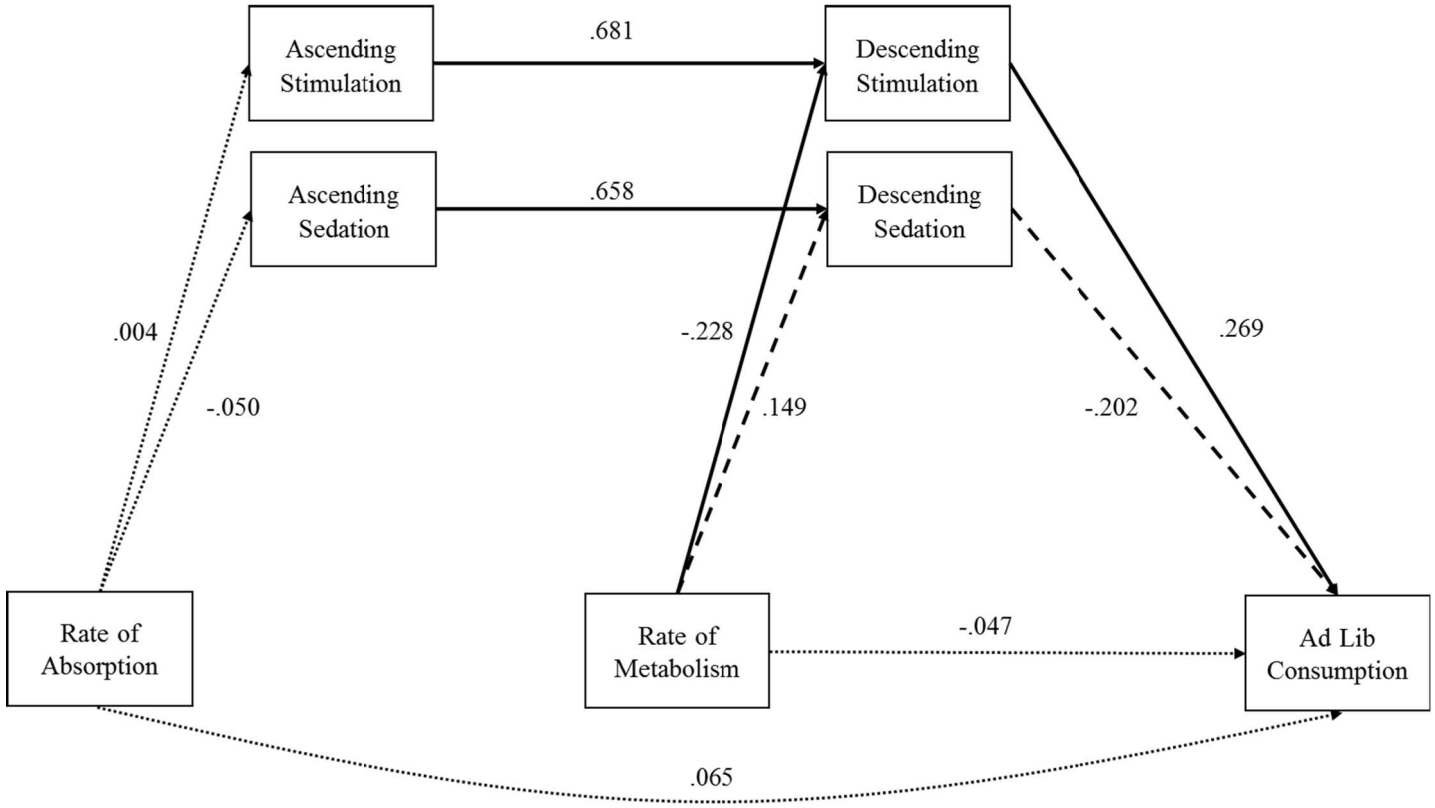

Figure 20. Results of Model 8 showing ascending and descending limb effects on ad-lib consumption.

Note. All values are standardized path coefficients. Solid lines indicate significant paths ($p < .05$); dashed lines indicate marginally significant paths ($p < .10$); dotted lines indicate non-significant paths ($p > .10$).

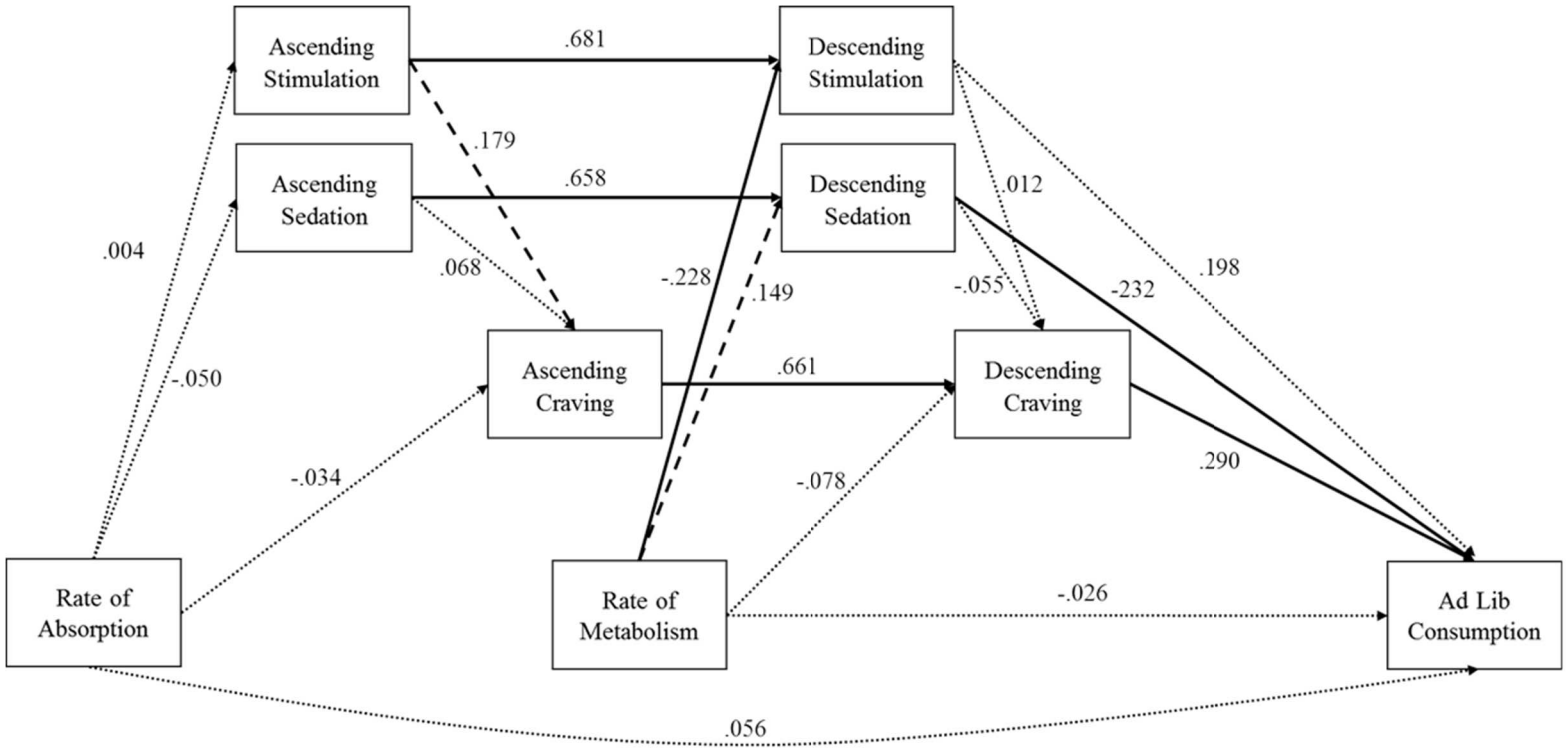

Figure 21. Results of Model 9 showing ascending and descending limb effects on craving and ad-lib consumption.

Note. All values are standardized path coefficients. Solid lines indicate significant paths ($p < .05$); dashed lines indicate marginally significant paths ($p < .10$); dotted lines indicate non-significant paths ($p > .10$).

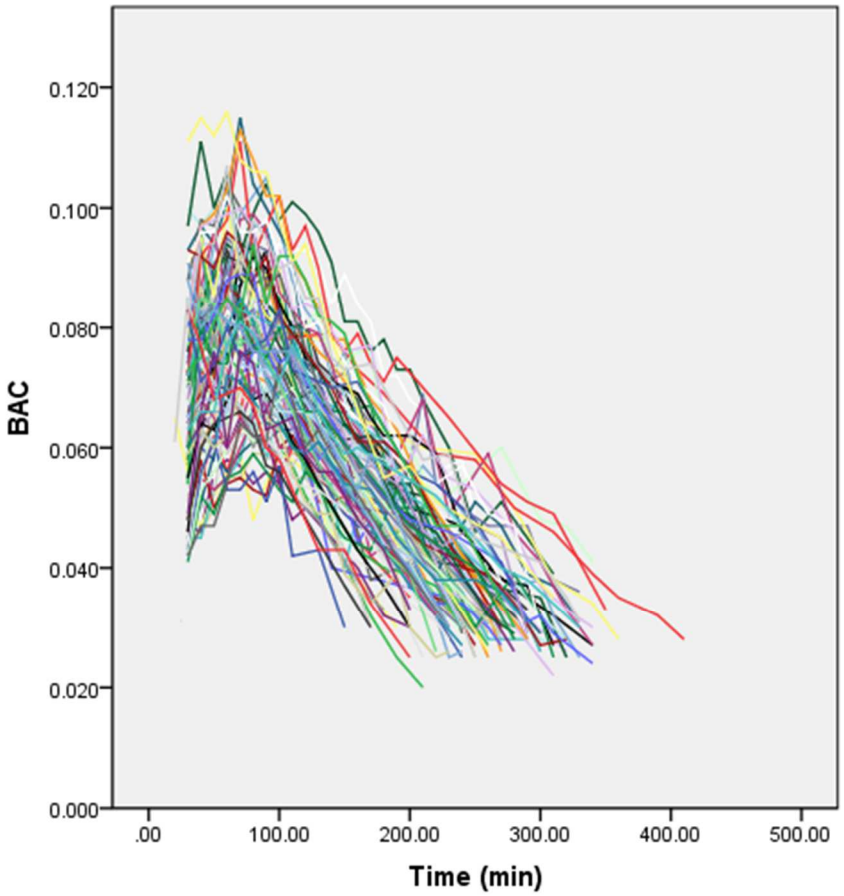

Figure 22. Blood alcohol concentration curves as a function of time for all participants.

APPENDIX A

MEASURES

DEMOGRAPHIC INFORMATION

Today's Date: ____ / ____ / ____ (mm/dd/yy)

Birthdate: ____ / ____ / ____ (mm/dd/yy)

Age: _____ years

Weight: _____ lbs.

Sex:
- ❑ Male
- ❑ Female

Marital Status:
- ❑ Single
- ❑ Married/Co-habitating
- ❑ Separated/Divorced

It is possible for an individual to have both an ethnic and racial identity. Please ✓ one in each category below.

Ethnic Identity [please ✓ one]:
- ❑ Hispanic or Latino
- ❑ Not Hispanic or Latino

Racial Identity [please ✓ one]:
- ❑ American Indian/Alaska Native
- ❑ Asian
- ❑ Native Hawaiian or Other Pacific Islander
- ❑ Black or African American
- ❑ White/Caucasian
- ❑ Other: _____

Highest level of education you have completed?
- ❑ 12th grade, no diploma
- ❑ High school diploma or equivalent (GED)
- ❑ Diploma or certificate from vocational, technical, trade school beyond high school level
- ❑ In college, but have not received degree:
  - ↳ What is your class standing?
    - ❑ Freshman
    - ❑ Sophomore
    - ❑ Junior
    - ❑ Senior
- ❑ Associate's degree
- ❑ Bachelor's degree
- ❑ In graduate school, but have not received degree
- ❑ Master's degree
- ❑ Doctoral degree (e.g., Ph.D., EdD)
- ❑ In professional program, but have not received degree
- ❑ Professional degree (e.g., MD, JD)

Most recent semester's G.P.A.:

_____

Estimated family income before taxes:
- ❑ Under $16,000
- ❑ $16,000 - $19,999
- ❑ $20,000 - $29,999
- ❑ $30,000 - $39,999
- ❑ $40,000 - $49,999
- ❑ $50,000 - $59,999
- ❑ $60,000 - $69,999
- ❑ $70,000 - $79,999
- ❑ $80,000 - $89,999
- ❑ $90,000 - $99,999
- ❑ $100,000 - $149,999
- ❑ $150,000 - $199,999
- ❑ $200,000 - $299,999
- ❑ $300,000 - $499,999

❑ $500,000 or more

Mother's Occupation:

_____

Father's Occupation:

_____

Approximately how much spending money (not devoted to bills) do you have each month?

AGE OF FIRST USE

INSTRUCTIONS: Please answer the following questions as best you can.

1. At what age did you first use alcohol without the permission of your parents?
   _____

2. At what age did you first get drunk?
   _____

FAGERSTRÖM TEST OF NICOTINE DEPENDENCE

1. Do you smoke?

   ❑ Yes ❑ No (do not answer questions 2 through 9; click the REVIEW and SUBMIT button, then click NEXT)

2. How soon after you wake up do you smoke your first cigarette?

   ❑ Within 5 minutes ❑ 6-30 minutes ❑ 31-60 minutes ❑ After 60 minutes

3. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in cinema, etc.)?

   ❑ Yes ❑ No

4. Which cigarette would you hate most to give up?

   ❑ The first one in the morning ❑ All others

5. How many cigarettes per day do you smoke?

   ❑ 10 or less ❑ 11-20 ❑ 21-30 ❑ 31 or more

6. Do you smoke more frequently during the first hours after waking than during the rest of the day?

   ❑ Yes ❑ No

7. Do you smoke if you are so ill that you are in bed most of the day?

   ❑ Yes ❑ No

8. When did you smoke your last cigarette? (note whether the time listed is AM or PM) _____

9. What is the current time? _____

FAMILY TREE QUESTIONNAIRE

INSTRUCTIONS: For each relative listed below, we want you to categorize their drinking behavior into one of five categories. Only include blood relatives; that is, relatives by birth. Not included would be those adopted, half-siblings, and step-relatives.

Code each relative using ONE of the following five codes:

1. **NEVER DRANK**: A person who (has) never consumed alcohol beverages (i.e., a lifelong abstainer; teetotaler).

2. **SOCIAL DRINKER**: A person who drinks moderately and is not known to have a drinking problem.

3. **POSSIBLE PROBLEM DRINKER**: A person who you believe or were told might have (had) a drinking problem but whom you are not certain actually has (had) a drinking problem.

4. **DEFINITE PROBLEM DRINKER**: Only include here persons who either are known to have received treatment of a drinking problem (including being a regular member of Alcoholics Anonymous), or who are known to have experienced several negative consequences of their drinking.

5. **NO RELATIVE**: Only applicable for brothers and sisters.

6. **DON'T KNOW/DON'T REMEMBER**

FAMILY TREE QUESTIONNAIRE (CONT.)

	Never Drank	Social Drinker	Possible Problem Drinker	Definite Problem Drinker	No Relative	Don't Know/Don't Remember
Maternal Grandmother (Mother's Mother)						
Maternal Grandfather (Mother's Father)						
Paternal Grandmother (Father's Mother)						
Paternal Grandfather (Father's Father)						
Mother						
Father						
Brother (1)						
Brother (2)						
Brother (3)						
Sister (1)						
Sister (2)						
Sister (3)						
You						

YOUNG ADULT ALCOHOL CONSEQUENCES QUESTIONNAIRE

INSTRUCTIONS: Please circle **YES** if you have ***ever*** experienced any of the statements below. Please circle **NO** if you have ***never*** experienced the situation.

1. While drinking, I have said or done embarrassing things. **YES** **NO**

2. My drinking has created problems between myself and my significant other/parents, or other near relatives. **YES** **NO**

3. I have become rude, obnoxious, or insulting after drinking. **YES** **NO**

4. My significant other/parents have complained to me about my drinking. **YES** **NO**

5. While drinking, I have said harsh or cruel things to someone. **YES** **NO**

6. I have said things while drinking that I later regretted. **YES** **NO**

7. I often drank more than I originally had planned. **YES** **NO**

8. I have spent too much time drinking. **YES** **NO**

9. I often have ended up drinking on nights when I had planned not to drink. **YES** **NO**

10. I often have found it difficult to limit how much I drink. **YES** **NO**

11. I have tried to quit drinking because I thought I was drinking too much. **YES** **NO**

12. I often have thought about needing to cut down or to stop drinking. **YES** **NO**

13. I have felt badly about myself because of drinking. **YES** **NO**

14. I have been unhappy because of my drinking. **YES** **NO**

15. I have felt guilty about my drinking. **YES** **NO**

16. Drinking has made me feel depressed or sad. **YES** **NO**

17. Because of my drinking, I have not eaten properly. **YES** **NO**

18. I have been less physically active because of my drinking. **YES** **NO**

19. Because of my drinking, I have not slept properly. **YES** **NO**

20. My physical appearance has been affected by my drinking. **YES** **NO**

21. I have been overweight because of my drinking. **YES** **NO**

22. I haven't been as sharp mentally because of my drinking. **YES** **NO**

23. I have not had as much time to pursue activities or recreation because of drinking. **YES** **NO**

24. I have had less energy or felt tired because of my drinking. **YES** **NO**

25. I have driven a car when I knew I had too much to drink to drive. **YES** **NO**

26. I have taken foolish risks when I have been drinking. **YES** **NO**

27. I have gotten into physical fights because of drinking. **YES** **NO**

28. I have damaged property or done something disruptive like setting off a fire alarm, or other things like that after drinking. **YES** **NO**

29. As a result of drinking, I neglected to protect myself or partner from an STD or unwanted pregnancy. **YES** **NO**

30. When drinking, I have done impulsive things that I regretted later. **YES** **NO**

31. My drinking has gotten me into sexual situations I later regretted. **YES** **NO**

32. I have injured someone else while drinking or intoxicated. **YES** **NO**

33. The quality of my work or school work has suffered because of drinking. **YES** **NO**

34. I have gotten into trouble at work or school because of drinking. **YES** **NO**

35. I haven't gone to work or have missed class because of drinking, a hangover, or other illness caused by drinking. **YES** **NO**

36. I have neglected obligations to family, work, and/or school because of drinking. **YES** **NO**

37. I have received a lower grade on an exam or paper than I ordinarily would have because of drinking. **YES** **NO**

38. I have felt like I needed a drink after I woke up. **YES** **NO**

39. I have had "the shakes" after stopping or cutting down on drinking. **YES** **NO**

40. I have found that I needed larger amounts of alcohol to feel any effect, or that I could no longer get high/drunk on the amount that used to get me high/drunk. **YES** **NO**

41. I have felt anxious, agitated, or restless after stopping or cutting down on drinking. **YES** **NO**

42. I have had a hangover (headache, sick stomach) the morning after drinking. **YES** **NO**

43. I have passed out from drinking. **YES** **NO**

44. I have felt very sick to my stomach or thrown up after drinking. **YES** **NO**

45. I have woken up in an unexpected place after heavy drinking. **YES** **NO**

46. I've not been able to remember large stretches of time while drinking. **YES** **NO**

47. I have awakened the day after drinking and found I could not remember a part of the evening before. **YES** **NO**

48. I have had a blackout after drinking heavily. **YES** **NO**

TIMELINE-FOLLOWBACK INTERVIEW

The 30-day interval begins with the day prior to the run (i.e., yesterday). **Be sure to check the top of the calendar before you start—make sure it is marked with the correct day of the week and today's date.**

Instructions:

"The purpose of this task is to gather information about your drinking experiences during the past month. Using this calendar, we'll be starting with your more recent drinking episodes and go backward until the ____ of _____ (insert appropriate day and month). *For each drinking episode, I'll ask you how many standard drinks you consumed, and over what period of time. A conversion scale for standard drinks is listed here* (point to conversion scale). *Before we begin, do you have any questions?"* (Answer them as you are able, or consult supervisor). *Okay, let's begin."*

1. *"When was your most recent drinking experience?"*
   - Identify a specific date. Use key dates (e.g. holidays, university events) if he/she is unsure of date. Circle that number on the calendar.

2. *"Remembering the definition of a standard drink we just discussed, please tell me how many standard drinks you consumed. As before, please refer to the drink conversion chart to help you make this determination.*

   - Use conversion table and follow up questions for the specific type of drink to determine the number of standard drinks to the nearest ¼ drink (e.g., 2 ¼ drinks is recorded as 2.25).

   Follow-up Questions by Beverage Type

   Beer – Use the conversion chart to show them the various sizes of beer that are commonly served with 12 oz representing 1 standard drink.

   Bottles and Cans (12 oz, 16 oz tall boy)
   Cups (8 oz, 12 oz, and 16 oz)
   Glasses (12 oz, 16 oz, 22 oz)

   Wine – Use the conversion chart to show them the various quantities of wine that are commonly served with 5 oz representing 1 standard drink.

   Glass (5 oz, 3 oz fortified)
   Bottles (25 oz bottle = 5 standard drinks, 40 oz or 25 oz fortified bottle = 8 standard drinks)

Malt Liquors - Use the conversion chart to show them the various quantities of malt liquor that are served with 12 oz representing 1 standard drink.

Bacardi Silver, Smirnoff Ice (12 oz)
Mike's hard lemonade (11.2 oz, 24oz)
12 oz Mickey = 8 standard drinks, 25 oz (Liter) = 17 standard drinks, 40oz = 27 standard drinks

Mixed Drinks - Use the conversion chart to show them the glass sizes.

Also, point out the four factors (see below) to consider when estimating standard drinks for mixed drinks. Provide the following instruction the first time the participant reports consuming mixed drinks. Repeat this instruction as needed for the remaining drinking days.

"*Remember that the number of standard drinks in a mixed drink depends on the following factors: 1) size of the glass, 2) type of alcohol, 3) type of drink, and 4) strength of the drink. Please keep these factors in mind when estimating the number of standard drinks you consumed on each day."*

3. "*Over what period of time did you drink?"*
   - Identify a specific length of time to the nearest ½ hour. If the participant gives a more specific time frame ask them to indicate to the nearest 30-minute interval (e.g., 3 1/2 hours is recorded as 3.5).

BIPHASIC ALCOHOL EFFECTS SURVEY

Instructions: The following adjectives describe feelings that are sometimes produced by drinking alcohol. Please rate the extent to which drinking alcohol has produced these feelings in you at the present time.

	Not At All										Extremely
Difficulty Concentrating	0	1	2	3	4	5	6	7	8	9	10
Down	0	1	2	3	4	5	6	7	8	9	10
Elated	0	1	2	3	4	5	6	7	8	9	10
Energized	0	1	2	3	4	5	6	7	8	9	10
Excited	0	1	2	3	4	5	6	7	8	9	10
Heavy Head	0	1	2	3	4	5	6	7	8	9	10
Inactive	0	1	2	3	4	5	6	7	8	9	10
Sedated	0	1	2	3	4	5	6	7	8	9	10
Slow Thoughts	0	1	2	3	4	5	6	7	8	9	10
Sluggish	0	1	2	3	4	5	6	7	8	9	10
Stimulated	0	1	2	3	4	5	6	7	8	9	10
Talkative	0	1	2	3	4	5	6	7	8	9	10
Up	0	1	2	3	4	5	6	7	8	9	10
Vigorous	0	1	2	3	4	5	6	7	8	9	10

ALCOHOL URGE QUESTIONNAIRE

INSTRUCTIONS: Indicate how much you agree or disagree with the following statements AT THE PRESENT TIME.

		Strongly Disagree						Strongly Agree
1)	All I want to do now is have a drink	1	2	3	4	5	6	7
2)	I do not need to have a drink now	1	2	3	4	5	6	7
3)	It would be difficult to turn down a drink this minute	1	2	3	4	5	6	7
4)	Having a drink right now would make things seem perfect	1	2	3	4	5	6	7
5)	I want a drink so bad I can almost taste it	1	2	3	4	5	6	7
6)	Nothing would be better than a drink right now	1	2	3	4	5	6	7
7)	If I had the chance to have a drink, I don't think I would drink it.	1	2	3	4	5	6	7
8)	I crave a drink right now.	1	2	3	4	5	6	7