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Investigating a Genetically Informed Enhanced Reinforcement Model of Alcohol Involvement: A Prospective Analysis

Scott D. Martin
University of Rhode Island

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INVESTIGATING A GENETICALLY INFORMED
ENHANCED REINFORCEMENT MODEL OF
ALCOHOL INVOLVEMENT: A PROSPECTIVE
ANALYSIS

BY
SCOTT D. MARTIN

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
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IN
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ABSTRACT

Enhanced reinforcement has figured prominently in etiologic models of alcohol involvement and may be of particular relevance in adolescence and emerging adulthood. We prospectively examined an enhanced reinforcement model in a sample of emerging adults and augmented the model with a promising candidate gene, OPRM1, which has demonstrated associations with both alcohol outcomes and psychosocial factors comprising the enhanced reinforcement model. We examined whether a putatively functional polymorphism in the OPRM1 gene was associated with heavy episodic drinking (HED) and negative consequences from drinking across four years via a number of intervening psychosocial factors, including behavioral undercontrol, subjective responses to alcohol, and cognitive factors (alcohol expectancies).

Participants ($N = 1,014$) were recruited prior to college matriculation for a randomized trial of two alcohol preventive interventions and were assessed via telephone surveys at baseline, and 10-, 22-, and 46-months. Retention rates were 90.8% of randomized students at 10-months and 84.0% at 22-months. The 46-month assessment that was later added had a retention rate of 62.0%. At Wave 4, 521 students provided a saliva sample for DNA analysis. Participants were considered “at-risk” if they carried at least one copy of the OPRM1 putative risk allele (the G allele of the A118G SNP).

A series of growth curve models tested growth in two outcomes, HED and consequences, across the college years. Unconditional models suggested the functional form of HED was well captured by a quadratic growth model with an intercept, and

linear and quadratic slope factors. Unconditional models suggested the functional form for the consequences outcome was linear with freely estimated time points for the linear slope factor. Gender and intervention conditions were included as exogenous factors along with family history (FH) and OPRM1 statuses. Behavioral undercontrol (BU), and subjective effects (SE) were included as mediators of FH and OPRM1 with activity enhancement expectancies (EXP) estimated as mediators of BU and SE effects. With the inclusion of direct paths from BU and SE to the intercept and slopes, model fit was acceptable for both models tested (CFI = .93, RMSEA = .056, for HED and CFI = 0.94, RMSEA = 0.055 for consequences). BU, EXP, and SE demonstrated significant positive associations with the intercept of HED, while only SE prospectively predicted the first growth factor. Indirect effects tested between family history and initial levels of HED were significant, indicative of partial mediation. Female gender and EXP were positively associated and SE was negatively associated with the second growth factor in the HED model. BU, EXP and SE were associated with the intercept and growth factor in the consequences model such that individuals with disinhibited personality traits and positive alcohol expectancies were susceptible to more initial problems and an increase in problems over time. However, SE was negatively associated with the growth of problems over time, suggesting that those with less sensitivity to alcohol may experience less change in problems over time. Indirect effects in the consequences model were also significant, indicative of partial mediation between FH and alcohol use consequences. OPRM1 risk was not associated with any of the model's factors. Findings provide modest support for an enhanced

reinforcement model and extend prospective evidence for the salience of the personality and cognitive factors tested in this model.

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CHAPTER 1

INTRODUCTION

Alcohol consumption relates to a variety of behaviors and consequences. Behaviors of consumption, including the quantity, frequency and pattern of alcohol use, and alcohol's effects on physiological, psychological and social factors can lead to negative consequences. Some of the heaviest rates of drinking occur during emerging adulthood (ages 18-25) (American College Health Association, 2011; Hingson, Zha, & Weitzman, 2009; Johnston, O'Malley, Bachman, & Schulenberg, 2010; Knight, Wechsler, Kuo, Weitzman, & Schuckit, 2002; Substance Abuse and Mental Health Services Administration, 2009) with 69.7 percent of American's between the ages of 19 and 28 currently using alcohol (at least one drink in the past 30 days) and 36.7 percent of young adults in this age bracket being "binge", or heavy episodic, drinkers (5 or more drinks in a row in the last 2 weeks) (Johnston et al., 2010). Young adults enrolled in college full time are more likely than their peers not enrolled full time to use alcohol (Johnston et al., 2010; Substance Abuse and Mental Health Services Administration, 2009). According to Knight et al. college students report high rates of alcohol abuse and dependence (2002). Specifically, they found that 31 percent of college students endorsed criteria for alcohol abuse, 6 percent endorsed criteria for alcohol dependence and students who were frequent heavy episodic drinkers had 13 times greater odds for abuse and 19 times greater odds for dependence (Knight et al., 2002).

Matriculation into college is typified by increases in alcohol consumption and associated negative consequences (Sher & Rutledge, 2007). Of the college students who do drink alcohol, half report experiencing serious negative consequences including, but not limited to, doing something they later regretted, getting in trouble with the police, having unwanted sex and physically injuring themselves and others (American College Health Association, 2009). In the U.S., it is estimated that approximately 1,825 annual deaths and more than 796,000 violent and sexual assaults are linked to alcohol use in the college student population (Hingson, Zha, & Weitzman, 2009).

These epidemiologic data highlight the alarming prevalence of alcohol use and misuse among “emerging adults” between 18 and 25 years of age, particularly among college students. They also underscore the importance of better understanding the complex etiologic pathways of alcohol use and misuse among emerging adults to assist in further developing and refining interventions aimed at reducing the acute and chronic effects of alcohol misuse in this population. To this end, the current study will prospectively investigate an enhanced reinforcement etiologic sub-model of alcohol involvement proposed by Sher (1991). We will also investigate further whether variation in a candidate gene (OPRM1), associated with alcohol reinforcement, is associated with the psychosocial factors comprising the enhanced reinforcement model, as well as alcohol use and problems. Next, models of vulnerability will be reviewed along with research examining associations between alcohol outcomes and the variables comprising the etiologic model proposed in this study, the enhanced reinforcement sub-model.

Models of Vulnerability

The notion that there is no single “type” of alcoholism or simple etiologic pathway for the development of alcohol misuse is widely accepted (Leonard & Blane, 1999; Sher, 1991). Years of research on alcohol vulnerability has investigated the contributions of biological, psychological and social influences on alcohol use. This research has developed the consensus among contemporary etiologic models that alcohol misuse and alcohol use disorders (AUDs) are caused and exacerbated by an array of biopsychosocial factors whose combined associations and influences vary across the life span (Leonard & Blane, 1999; Sher, 1991; Zucker, 1987; Zucker, 2006).

Vulnerability studies have sought to identify mechanisms of risk for alcohol misuse and given the long-recognized heightened risk of children of alcoholics (COAs), this group has often been the focus of these studies. Behavioral genetics studies have consistently supported a role for genetic factors in familial transmission of alcoholism (Cloninger, Bohman, & Sigvardsson, 1981; Cotton, 1979; Goodwin, 1988; Kaprio, Koshenvuo, & Langinvainio, 1987; Sher, 1991). The evidence that genetic factors are associated with responses to drinking and the development of alcohol misuse is beyond dispute (Ball & Murray, 1994; McGue, 1994; 1999; Merikangas, 1990). However, the most influential genes affecting alcohol outcomes have not been well elucidated and research linking candidate genes, genes implicated in contributing to a particular phenotype (e.g. disease) (National Institute on Alcohol Abuse and Alcoholism, 2003), with etiologically relevant psychosocial factors is one approach to substantiating these genes of interest (Dick, Lattendresse, & Riley, 2011).

Accordingly, substantial gaps remain in understanding the specific genetic components influential to alcohol misuse, but the candidate gene approach is promising and continues to elucidate new genes of interest relevant to alcohol studies. Genetics alone do not account for the direct expression of behavior, however. According to McGue “there are numerous intervening steps between primary gene product (protein synthesis) and observable behavior. Genetic influences on alcoholism risk might reflect mechanisms ranging from ethanol sensitivity to heritable personality characteristics” (1999, p. 373).

Prospective examination of etiologic pathways through which susceptibility (e.g., family history and specific genotype) factors affect intervening psychosocial variables and alcohol outcomes is critically important for both furthering knowledge of the etiology of alcohol use and misuse and for informing preventive interventions. Sher (1991) introduced a comprehensive model of simple and more complex pathways through which familial risk may be transmitted. In this overarching model, family history is mediated by several broad categories including personality, cognitive processes, biological influences and familial and other environmental considerations (1991). Sher’s overarching model is also broken down into less complex inter-related sub-models labeled “enhanced reinforcement”, “deviance-proneness”, and “negative affect”. As noted, the current research will focus on the enhanced reinforcement sub-model and will incorporate examination of a candidate gene, OPRM1, which has been linked to reinforcing effects to alcohol (Ray & Hutchison, 2004) along with personality and cognitive factors.

Sher states “that family history of alcoholism is causally related to increased reinforcement value from alcohol which in turn leads to an increased likelihood of developing alcohol problems” (1991, p.135). In his enhanced reinforcement model the pathways from family history to alcohol involvement are mediated by temperament/personality, ethanol sensitivity, and alcohol expectancies. Simply put, central to this model is that the development of alcohol problems and disorders are related to the reinforcement value from alcohol, and specific personality traits, ethanol sensitivity and cognitive factors included in this study’s model are those related to the reinforcing effects of alcohol use, as will be discussed further below.

Integrating Sher’s (1991) model with research on the candidate gene OPRM1, Figure 1 proposes a genetically-informed enhanced reinforcement sub-model of alcohol involvement among an emerging adult population. An emerging adult sample is particularly well suited to such an examination given the high levels of alcohol use and misuse in this subpopulation and due to evidence that positive reinforcement motives may be particularly important in adolescent and emerging adult populations (Kuntsche, Knibbe, Gmel, & Engles, 2006; Read, Kahler, Wood, Maddock, & Palfai, 2003). Next, we briefly describe the overall sub-model.

Figure 1. A Genetically-Informed Enhanced Reinforcement Model

Figure 1. Personality= behavioral undercontrol; Subjective Response= ethanol sensitivity; Motives= enhancement motives; Expectancies= activity enhancement alcohol expectancies; Alcohol involvement= consumption and consequences intercept and slope.

As can be seen in Figure 1, family history of alcoholism and genetic variation in the OPRM1 gene are exogenous factors with associations on alcohol involvement (alcohol consumption and negative consequences) via a number of intervening psychosocial factors. Specifically, consistent with Sher's (1991) enhancement reinforcement model, family history effects on alcohol outcomes are purportedly mediated by "behavioral undercontrol" personality traits and subjective effects to alcohol (ethanol sensitivity). In turn, associations between personality and subjective effects and alcohol outcomes are mediated by alcohol expectancies that have been purported to be final common pathways through which more distal biopsychosocial factors influence alcohol use and misuse (Cooper, Frone, Russell, & Mudar, 1995; Goldman, 1994). While not a part of Sher's (1991) formulation, the inclusion of

OPRM1 in the model depicted in Figure 1 builds on a nascent but growing body of research on candidate genes important to understanding alcohol use and misuse. This model hypothesizes that genetic variation in the OPRM1 gene along with family history will be related to alcohol outcomes indirectly via behavioral undercontrol personality traits, subjective effects to drinking, and alcohol expectancies. A review of the existing research in support of the hypothesized associations between constructs incorporated within the enhanced reinforcement model and their etiologic evidence will be discussed in greater detail below.

Etiologic Evidence for Sub Model Factors

Family History.

It has long been recognized that alcohol use disorders tend to run in families (Cotton, 1979). For example, Dawson, Harford and Grant (1992) reported that individuals with an alcoholic first-degree relative (i.e., parent, sibling, or children) were at 86 percent greater risk for alcohol dependence than those without a family history of alcoholism. While “high risk” (e.g., oversampling on family history) designs are incapable of resolving the extent to which familial transmission of alcohol use disorders are genetically and environmentally influenced, there is considerable evidence from behavior-genetic research in support of genetic influences on alcohol use and misuse, as well as consensus regarding the need to consider the joint and interacting effects of genetic and environmental factors (McGue, 1994; McGue, 1999; Rose & Dick, 2004-2005; van der Zwaluw & Engels, 2009). Research utilizing high-risk designs) has observed cross-sectional (Sher, Walitzer, Wood, & Brent, 1991) and prospective effects (Chassin, Curran, Hussong, & Colder, 1996) on alcohol use

outcomes. Moreover, consistent with the enhanced reinforcement sub model, in cross-sectional analyses using structural equation modeling, Sher et al. (1991) found that family history status was associated with behavioral undercontrol traits, which, in turn, were associated with alcohol expectancies, which predicted alcohol involvement. Similarly, Schuckit et al. found significant associations among first degree relatives and subjective effects to alcohol (Schuckit et al., 2005), suggesting that subjective effects may be one of the mechanisms through which familial influences are transmitted. Longitudinal evidence has shown family history of substance use disorders, including alcohol use disorders, to be directly related to behavioral disinhibition and in turn to the development of substance use disorders (Kirisici, Vanyukov, & Tarter, 2005).

OPRM1.

A great deal of recent research and theory has pointed to candidate gene and genome-wide association studies as vital for furthering understanding of the development of alcohol use disorders (Cannon & Keller, 2003; Gottesman & Gould, 2003; O'Brien, 2008) although concern has been expressed about the ultimate viability of candidate gene approaches (Risch et al., 2009). While a review of this literature is beyond the scope of the current study, based on its relevance for reinforcement models of drinking, we include the mu-opioid (μ -opioid) receptor gene (genetic locus OPRM1) in the model to be tested here. OPRM1, specifically, the single nucleotide polymorphism (SNP) A118G of the OPRM1 gene (rs1799971), has been studied as a primary genotypic influence on alcohol use and misuse. Variations in OPRM1 have been tested and shown to be associated with alcohol use disorders (AUDs) (Kranzler,

Gelernter, O'Malley, Hernandez-Avila, & Kaufman, 1998; Miranda et al., 2010; Oroszi & Goldman, 2004; Ray & Hutchison, 2004; Schinka et al., 2002; Zhang et al., 2006), subjective effect to alcohol (Ray, & Hutchison, 2004) and alcohol craving, consumption and expected effects (Ehlers, Lind, & Wilhelmsen, 2008; van den Wildenberg et al., 2007; Wiers, Rinck, Dictus, & van den Wildenberg, 2009).

The μ -opioid receptor facilitates the analgesic effects of opioids in the brain, and influences the behavioral changes associated with physiologic dependence in animals (Matthes et al., 1996). The μ -opioid receptor also influences the dopaminergic system and its associated pathways (Adinoff, 2004). Dopaminergic neurons, as described by Chinta and Andersen, play an important role in controlling multiple brain functions including a wide array of behavioral processes such as mood, reward, addiction, and stress (Chinta & Andersen, 2005).

According to Adinoff the compulsive drive toward drug use is complemented by deficits in impulse control and decision making (2004) and Derringer et al. showed that dopamine genes are associated with sensation-seeking (Derringer et al., 2010) which substantiates the hypothesized pathway from OPRM1 to behavioral undercontrol in this study's model. Adinoff also states that "dopaminergic activation occurs in the presence of unexpected and novel stimuli (either pleasurable or aversive) and appears to determine the motivational state of wanting or expectation" (2004, p 305), which supports OPRM1's pathway to motivation.

In OPRM1 the G allele is functionally different. The G allele variant binds the amino acid beta-endorphin three times more strongly than the A variant (Bond et al., 1998). The beta-endorphin is an endogenous morphine in the body, or an opioid

peptide neurotransmitter found in the central and peripheral nervous systems. One of its functions is to numb the body and modulate the feeling of pain after experiencing trauma. Individuals with the G allele may display behavioral difference because of a heightened sensitivity to μ -receptors. This means that individuals with the G allele may be more sensitive to the subjective effects of alcohol such as euphoria, as was observed by Ray and Hutchison (2004). Accordingly, individuals with the G allele are considered to be “at risk” for higher sensitivity to ethanol in support of the hypothesized pathway from OPRM1 to ethanol sensitivity in our model.

The allele frequencies for the G variant differ by population (Kidd, 2011; Oroszi, & Goldman, 2004). East Asians have the highest allelic count ranging from .20 to .55, people with European decent range from .10 to .30, Hispanics range from .06 to .30 and African-Americans have a frequency count at about .04 (Kidd, 2011; Oroszi, & Goldman, 2004).

Several studies looking at OPRM1, however, have not found substantial evidence to support OPRM1’s etiological relevance to alcohol misuse (Arias et al., 2006; Bergen et al., 1997; van der Zwaluw et al., 2007). Inconsistent findings related to OPRM1’s influence on alcohol misuse suggest the need of further study, particularly as part of larger etiologic models. Therefore inclusion of OPRM1 in the enhanced reinforcement model is valuable for analyzing OPRM1’s influence, if any, on alcohol outcomes.

Personality.

In more contemporary etiologic models, personality is viewed as one of many factors influencing alcohol misuse (Sher et al., 1999). While it is widely agreed that

there is no such thing as an “alcoholic personality”, decades of research attest to the etiologic relevance of personality traits to alcohol use and misuse (Leonard & Blane, 1999; Schuckit, Klein, Twitchell, & Smith, 1994). Evidence from both cross-sectional and prospective research for the influence of personality on alcohol use and misuse is considerable, particularly with respect to traits related to “behavioral undercontrol” (described below).

There is good evidence from cross-sectional and prospective studies beginning before the age of onset of drinking that traits related to “behavioral undercontrol” are the most etiologically relevant trait dimensions associated with the development of alcohol use disorders (Sher, & Littlefield, 2008; Sher, 1991), including the development of alcohol dependence and abuse (Caspi, Moffitt, Newman, & Silva, 1996; Rutledge & Sher, 2001; Schuckit & Gold, 1988; Schuckit et al., 1994; Schuckit & Smith, 2006a; Sher, Bartholow, & Wood, 2000). Behavioral undercontrol (BU) includes a wide range of facets (Miller & Carroll, 2006) which are perhaps best represented by impulsivity, disinhibition, sensation seeking, novelty seeking, and psychoticism (Sher, Trull, Bartholow, & Vieth, 1999; Zuckerman, Kuhlman, & Camac, 1988).

Psychoticism, labeled by Eysenck (1947), should not be confused with the clinical diagnoses of psychotic disorders or psychotic episodes. Rather, psychoticism was originally framed in relation to trait features rooted in the characteristics of tough-mindedness, non-conformity, inconsideration, recklessness, hostility, anger and impulsiveness (Eysenck, 1947). Psychoticism has received cross sectional and longitudinal support for its role in the etiology of alcohol disorders (Sher et al., 2000).

Impulsivity is generally marked by a lack of planning and the tendency to act without thinking and sensation seeking is most often described as experience seeking, or the willingness to take risks for the sake of excitement or novel experience (Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1993). The general sensation seeking trait is related to an uninhibited, nonconforming, impulsive, dominant type of extraversion (Zuckerman, Bone, Neary, Mangelsdorff, & Brustman, 1972). Both impulsivity and sensation seeking have been associated with alcohol-related problems (Caspi et al., 1996; Cloninger, Sigvardsson, & Bohman, 1988; Hawkins, Catalano, & Miller, 1992; Schuckit, 1998; Sher et al., 2000; Zucker, Fitzgerald, & Moses, 1995).

Thus, the broad personality dimension of behavioral undercontrol capturing individual differences in the ability to regulate impulsive and disinhibited tendencies is significant with respect to models of enhanced reinforcement (Leonard & Blane, 1999; Sher, 1999). Impulsivity, sensation seeking and psychoticism are among the most etiologically relevant facets comprising the behavioral undercontrol factor used in the model of this research (Leonard & Blane, 1999; Miller & Carroll, 2006; Sher, 1991). The behavioral undercontrol factor in the proposed enhanced reinforcement model will be comprised of individual facets of impulsivity, sensation seeking and psychoticism. The influence of behavioral undercontrol personality traits on alcohol misuse has been shown to be mediated by expectancies (Schuckit & Smith, 2006a; Sher, Walitzer, Wood, & Brent, 1991), therefore the proposed enhanced reinforcement model posits that behavioral undercontrol's influence on alcohol outcomes will be indirect through alcohol expectancies as detailed in a subsequent section.

Ethanol Sensitivity.

Individuals differ in their sensitivity, or level of response, to ethanol. Initial research in this area noted that among individuals of Asian ethnicity, genetic heterogeneity in alcohol metabolizing genes (ADH, ALDH) were associated with aversive responses to alcohol including facial flushing, heart palpitations, and nausea (Mizoi et al., 1979; 1983). In contrast to this heightened sensitivity to negative effects, some people exhibit a heightened sensitivity to reinforcing effects of alcohol, but genetic variation associated with this type of response is not well elucidated, making it an important goal of the present research.

A low level of response to alcohol is described by either a low intensity of reaction to ethanol at a given blood alcohol concentration (BAC) via an administered lab test known as an alcohol challenge (Schuckit & Gold, 1988; Schuckit & Smith, 2000), or as a retrospective self report from earlier in life reporting the need for more drinks before an effect from alcohol was felt (Schuckit, Smith, & Tipp, 1997; Schuckit, Tipp, Smith, Wiesbeck, & Kalmijn, 1997). A high correlation between these measures was found by Schuckit et al. (1997) (.82, $p < .0001$). A decreased sensitivity to the effects of alcohol purportedly leads to heavier intake even among relatively light and infrequent drinkers and is thought to be indicative of genetically transmitted tolerance to alcohol (Schuckit et al., 2008a; Schuckit et al., 2008b). Multiple studies have shown that a lower level of response earlier in life predicted future heavier drinking and alcohol problems (Schuckit et al., 2008a; Schuckit et al., 2008b; Schuckit et al., 2009; Schuckit, 2009; Volavka et al., 1996).

Alternatively, as noted, some individuals have increased sensitivity to the effects of ethanol. This heightened sensitivity is included in Sher's enhanced

reinforcement sub-model (1991). In the enhanced reinforcement model heightened sensitivity to alcohol's positive reinforcing "psycho-stimulant" effects are invoked to explain increases in alcohol consumption (Conrad, Petersen, & Pihl, 1997). Sher posits a direct path from family history to ethanol sensitivity (increased sensitivity) in his sub-model because of the direct effects alcohol has on brain centers related to reward. Sher states,

Ethanol sensitivity is also posited to be related to cognitive dysfunction and temperament/personality. It is further proposed that pharmacologically mediated individual differences in ethanol sensitivity are translated into increased expectancies of reinforcement from alcohol with sufficient drinking experience. These expectancies are, in turn, thought to be the proximal mediator of drinking behavior (1991, pp 135-136).

According to Sher, individuals with an inherited heightened sensitivity to alcohol tend to have increased expectations of reinforcement from drinking. Accordingly, the enhanced reinforcement model in our study is congruent with Sher's hypothesis by positioning ethanol sensitivity between family history and cognitive factors, such as alcohol expectancies, which are briefly reviewed next.

Alcohol Expectancies

Alcohol expectancies, defined as beliefs about the cognitive, behavioral, and affective effects of drinking alcohol, have long been ascribed a significant role in the etiology of alcohol use and misuse (Goldman, Del Boca, & Darkes, 1999; Leigh, 1989). Moreover, expectancies have been hypothesized to be a final common pathway

through which more distal psychosocial factors, such as family history and personality are transmitted to behaviors.

Alcohol expectancies emerge during childhood, via vicarious learning (e.g., observation of alcohol's effects on family members and others) and are thought to increase and become more homogenous from childhood through adolescence (Christiansen, Goldman, & Inn, 1982; Miller, Smith, & Goldman, 1990). In contrast, among older adolescents, decreases in alcohol expectancies have been observed over time (Sher, Wood, Wood, & Raskin, 1996). Sher et al. (1996), in consideration of these developmental patterns, suggested that vicariously learned expectancies are initially strengthened by direct experience with alcohol, with additional direct experience leading to a tempering of expectancy strength. Using exploratory and confirmatory factor analytic approaches, numerous measures of alcohol expectancies have been developed and examined as correlates of alcohol use (Brown, Goldman, & Christiansen, 1985; Brown, Christiansen, & Goldman, 1987; Fromme, Stroot, & Kaplan, 1993; Kushner, Sher, Wood, & Wood, 1994). While a number of factors related to positive and negative alcohol expectancies have been identified in this research, of greatest relevance for investigation in the context of enhanced reinforcement are positive alcohol expectancies such as "activity enhancement" (Kushner et al., 1994). Expectancies for activity enhancement include statements like, "drinking makes many activities more enjoyable", and relate to positive hedonic experiences. Enhancement expectancies have received cross sectional and prospective support in their influence on alcohol use among emerging adults (Sher et al., 1996). The collection of cross-sectional and prospective research supports the etiologic

relevance of alcohol expectancies and the inclusion of activity enhancement expectancies in larger enhanced reinforcement models of alcohol use and misuse.

CHAPTER 2

PRESENT STUDY

As presented, contemporary etiologic models consistently propose that alcohol use and misuse are caused, maintained, and exacerbated by direct and indirect associations of an array of biological, psychological, and social factors that vary over time and developmental periods (Sher, 1991; Zucker, 1987; Zucker, 2006). Accordingly, the purpose of the present study is to prospectively test an influential etiologic sub-model proposing that enhanced reinforcement is important in understanding the development of alcohol use and misuse. As noted, given the prevalence of alcohol use and misuse in emerging adulthood, and previous research suggesting that positive reinforcement motivations are particularly salient in adolescence and emerging adulthood, the present sample is particularly well-suited to address this question. Moreover, the extension of Sher's (1991) sub model, to include consideration of variation in a candidate gene implicated in appetitive motivation for alcohol and other drugs, constitutes a potentially important advancement toward the integration of biological factors in etiologic models. As depicted in Figure 1 and further delineated in our proposed analyses, we will prospectively examine direct and indirect (mediational) relations between family history of alcoholism, genetic variation in OPRM1, behavioral undercontrol personality traits, subjective effects to alcohol, alcohol expectancies on multiple alcohol outcomes.

Consistent with the literature reviewed, several hypotheses are forwarded. It is hypothesized that the relationship between OPRM1 and family history of alcoholism and alcohol-related outcomes (negative consequences and heavy drinking) will be mediated by “behavioral undercontrol” personality traits and subjective effects to alcohol (ethanol sensitivity). In turn, associations between personality and subjective effects and alcohol outcomes will be mediated by alcohol expectancies. It is also hypothesized that OPRM1 will be positively associated with the trajectory of heavy drinking and alcohol problems, such that individuals with the G allele will exhibit higher levels of alcohol use and problems. These analyses will add to the general scientific understanding of alcohol use trajectories in an emerging adult/college student population. To our knowledge, the proposed research is both the first to comprehensively examine an enhanced reinforcement sub-model prospectively in a population with enhanced risk for alcohol misuse and to incorporate a functionally relevant and empirically supported candidate gene within the sub-model. Additionally, understanding how these specific factors influence alcohol use may assist in the development of interventions aimed at reducing the acute and chronic effects of alcohol misuse in this population perhaps through targeting factors included in this model.

CHAPTER 3

METHODOLOGY

Sample

As part of a larger study (Wood et al, 2010) in two successive cohorts, participants ($N = 1,014$ parent-student dyads) were recruited during the summer prior to matriculation at a mid-sized public northeastern university. The target population was entering full-time or part-time students ages 17-21.

Mean age at baseline was 18.4 with a standard deviation of 0.41. The sample was 57% female, 89% White, 5% Hispanic, 4% Black, 1% Asian, and 6% “other” (categories not mutually exclusive). The sample did not differ from the population of incoming students with respect to gender and ethnicity, but did differ in terms of race, chi-square (3, $N = 4940$) = 11.35, $p < .01$, with slightly less sample representation of African American (4.1% vs. 5.3%) and Asian American (1.2% vs. 2.9%) students as compared to the population from which they were drawn.

Follow up interviews were conducted at 10 and 22 months post baseline (Wave 2 and Wave 3 respectively). At the Wave 2 follow-up 90.8 % (921 students) were retained and 84.0% ($n = 852$) completed the 22 month follow up. At Wave 3, 797 participants consented to be contacted for future participation. In a fourth wave of data collection (46 months post baseline) 627 (61.8%) of the students who consented to be re-contacted were surveyed and saliva samples were collected from 524 students (51.7%) for DNA analysis.

Procedure

Procedural information is described in detail elsewhere (Wood et. al, 2010). Briefly, all participants provided consent or assent; parents provided consent for students under 18 years of age at baseline. Participants were surveyed and information verified and updated via telephone by the URI Survey Research Center (SRC) interviewers using a scripted, computer-assisted telephone interview (CATI) protocol. All procedures were approved by the university's Institutional Review Board.

Measures

Measures used in the current analyses were completed by students at baseline or at one or more follow up periods (10, 22 and 46 months). Mean scale scores were calculated for measures with more than two items and collected at more than one time point, except where otherwise indicated. Student participants provided demographic information regarding gender, age, race, ethnicity, intended fraternity/sorority involvement, and residential status. Study measures described below are taken from larger questionnaire batteries at each time point. Variables with multiple measures were included in the model as latent factors. Factor structures and confirmatory factor analysis results of those structures are presented in the results section below.

Family History (FH).

At Wave 1, a single item measure recommended by Crews and Sher (1992) was used to assess family history of alcoholism. Students were asked about both parents, "Do you think your (father/mother) is/was an alcoholic"? Crews and Sher (Crews & Sher, 1992) demonstrated that this global rating of both paternal and maternal alcoholism had excellent test-retest stability (assessed twice over a 10-day to

3-week test-retest interval), high inter-sibling agreement, and moderately high agreement with the corresponding self rating from the parent's report of problems with drinking. Crews and Sher's results also showed that this global item had acceptable sensitivity, specificity, kappa, and Y values. Family history status was coded as a categorical variable (0, 1, or 2) for individuals with neither parent identified as having alcoholism (0), either father or mother having alcoholism (1) or both father and mother having alcoholism (2). In the sample 79 people had a family history of alcoholism (15.56 percent of total sample, with 14.87 percent = one parent and 0.59 percent = both parents).

OPRM1.

Oragene DNA Self-Collection kit procedures were used to genotype 524 DNA-providing participants at Wave 4. Whenever possible, DNA was obtained on site by project staff using written protocols to ensure sample viability and strict attention to confidentiality. When this was not possible, DNA was obtained by self-collection and returned using procedures for protecting participant confidentiality. Single nucleotide polymorphisms (SNPs) were genotyped using an Illumina BeadXpress 384-snp panel following established protocols. Genetic risk is defined as having at least one copy of the OPRM1 putative risk allele, the G allele (Miranda et al., 2010; Ray & Hutchison, 2004). Data were dummy coded to indicate which individuals were "at risk" (1 = risk by presence of the G allele). Of those who provided DNA samples 140 had at least one copy of the G allele (27%), a proportion comparable to other samples (Kidd, 2011; Oroszi, & Goldman, 2004).

Behavioral Undercontrol.

Personality traits related to impulsivity and sensation seeking were measured at Wave 3 using the Impulsivity/Sensation Seeking Scale (ImpSS) (Zuckerman et al., 1993), with the sum score of 7 items measuring impulsivity ($\alpha = .67$) and 11 items measuring sensation seeking ($\alpha = .75$). There were originally 8 items of the impulsivity scale, but one had to be deleted due to a typographical error on the survey given to participants. The items for both scales had a true-false response format for whether the question “is true as applied to you” or “if false as applied to you” and includes questions such as, “I often do things on impulse” and “I like to do things just for the thrill of it”. Psychoticism (tough mindedness) was measured at Wave 3 as part of the Revised Eysenck Personality Questionnaire (EPQ-R) (Eysenck, 1988), a 57 item measure. The sum score from a psychoticism subscale of 17 items taken from the EPQ-R was used to measure psychoticism in the behavioral undercontrol factor ($\alpha = .54$).

Ethanol Sensitivity (Subjective Effects).

Ethanol sensitivity was collected at Wave 3 via self report. Four items of the Self-Rating of the Effects of Alcohol (SRE) scale ($\alpha = .87$) about the first five times one ever drank was used (Schuckit, Smith, & Tipp, 1997). Specifically, participants were asked how many drinks it took for them to: “begin to feel different”, “feel a bit dizzy, or begin to slur your speech”, “begin stumbling or walking in an uncoordinated manner”, and “pass out, or fall asleep when you did not want to” with reference to the first five times one ever drank alcohol. Response options were coded according to standard drinks. One standard drink was defined as one shot of liquor, 12 ounces of beer, or one 4-ounce glass of wine, and “in a row” was defined as one occasion

without any breaks of an hour or longer (Wood et al., 2010). The Self-Rating of the Effects of Alcohol scale has been shown to possess good test-retest reliability in studies conducted over multiple years and including multiple follow up assessments (Schuckit et al., 1997). Laboratory tests known as the “alcohol challenge”, in which participants consume alcohol inside the laboratory and the resulting effects closely tracked, have been strongly correlated to SRE self report measure (.82, $p < .0001$) (Schuckit et al., 1997). To be consistent with Sher’s (1991) sub model, lower SRE scores are indicative of a higher ethanol sensitivity (lower scores are equivalent to fewer drinks needed for an effect which is inferred as a high sensitivity to alcohol).

Activity Enhancement Alcohol Expectancies

From a larger scale of alcohol expectancies, activity enhancement alcohol expectancies were assessed at Wave 4 using a 9 item activity enhancement subscale measure (Kushner et al., 1994) ($\alpha = .87$). Sample items include, “drinking makes many activities more enjoyable” and “Drinking makes sports events (like football, basketball, car races) more enjoyable.” Individuals were asked to rate their personal expectations of the effects of alcohol on a 5 point scale (1 = Not at all, 2 = A little bit, 3 = Somewhat, 4 = Quite a bit, and 5 = A lot). As seen in Figure 2 the nine items were parceled into four indicators that loaded on the latent factor. Each parcel contained an average score.

Figure 2. Factor Structures of the Endogenous Latent Variables (Mediating Variables) in the Enhanced Reinforcement Sub-Model of Alcohol Use.

Figure 2. Activity Enhancement Expectancies: Parcel 1) alcohol tastes good & drinking adds enjoyment to a good meal; Parcel 2) drinking makes any celebration more enjoyable, drinking is a good way to kill time, & drinking makes many activities more enjoyable; Parcel 3) drinking can be exciting, & drinking makes sports events more enjoyable; Parcel 4) drinking helps me fall asleep at night, & drinking makes listening to music more enjoyable.

Alcohol Outcomes.

Alcohol consumption.

Two measures of alcohol consumption were used in the current study. Drinks per week were assessed with the Daily Drinking Questionnaire (DDQ; Collins, Parks, & Marlatt, 1985) asking about typical number of drinks on each day of the week and is included here for descriptive purposes only. Heavy episodic drinking was assessed (at baseline, 10, 22 and 46 months) by asking, via an open-ended response format, the number of times in the last month that students had consumed five or more drinks in a row (Wechsler, Lee, Kuo, & Lee, 2000).

Alcohol consequences

Alcohol consequences were assessed with a 17-item version of the Young Adult Alcohol Problems Screening Test (YAAPST) (Hurlbut & Sher, 1992). The YAAPST was administered at baseline, 10 months 22 and 46 months. The scale assessed the past 3-month frequency of alcohol consequences with response options ranging from 1 (no, not in the past 3 months) to 5 (10 or more times in the past 3 months). Consequences include, “have you gotten into physical fights when drinking?” and “have you ever been pressured or forced to have sex with someone because you were too drunk to prevent it?”, for example. The responses of each item were recoded as an estimate of the number of occurrences (e.g., response option “2” (1-3 times in past 3 months) recoded to 1.5 and response option “5” (10 or more times) recoded to “12.5”). Mean scores were then computed across the 17 recoded items (α 's = .81 - .87) (Wood et al., 2010).

Overview of Analyses

We utilized random effects longitudinal data analytic techniques that are particularly well suited for modeling behavior during developmental periods of change (Bollen & Curran, 2006; Rose, Chassin, Presson, & Sherman, 2000).

First, missing data and descriptive statistics are reviewed, then the results of confirmatory factor analysis (CFA) for the factor structure of the latent variables in this model are described. CFA results are followed by latent growth curve modeling. Initial models examined the model depicted in Figure 1, which assumes full mediation of family history and OPRM1. In addition to evaluation of initial models based on overall model fit criteria (detailed under “Latent Growth Curve Models,” tests of

hypothesized indirect effects were computed. Subsequent to these analyses, the full mediation models were compared to more saturated models (e.g., with additional direct paths to alcohol outcomes) in nested model comparisons.

CHAPTER 4

RESULTS

Missing Data

Analyses for systematic attrition for the first three waves have been conducted for this data (Wood et al., 2010). To extend these analyses to the final wave, Wave 4 survey completers ($n = 627$) were compared with non-completers ($n = 387$). Using χ^2 and t-tests for categorical and continuous variables, we observed no significant baseline differences on gender, race, ethnicity, weekly drinking, heavy drinking, or alcohol problems. Genotyped individuals consumed significantly fewer peak drinks at baseline ($p = .048$) but survey completers did not differ from non-completers on peak drinking. In sum, we found very limited evidence of systematic attrition (Wood et al., 2010). Latent growth curve models testing the study's substantive hypotheses were estimated using all available data, and all parameters were estimated using maximum likelihood estimation.

Descriptive Statistics

Univariate statistics were computed on all continuous variables included in analyses to assess normality and detect irregularities in the data (outliers, skewness and kurtosis). Maximum likelihood estimation procedures, which are robust to violations of normality (Singer & Willett, 2003), were used as part of our confirmatory factor analyses and latent growth curve modeling. Nonetheless, variables with marked departures from normality (e.g., skew > 2.0 and kurtosis > 4.0) received corrective

action (Tabachnick & Fidell, 2007). Several of the outcome variables departed from a normal distribution. These variables were, heavy episodic drinking, alcohol consequences, and one of the variables in the ethanol sensitivity factor, the Self-Rating of the Effects of Alcohol scale, question two. These outcome variables were log transformed (Tabachnick, & Fidell, 2007) and normal distributions of each variable resulted. Transformations were applied to the outcome variables for analysis of the models proposed in this study, but reported below are the non transformed results of drinking measures outcomes for interpretability.

Three observations in question two of the SRE scale were identified as extreme outliers. These three observations were adjusted to be within 1.0 of the furthest value above the 75th percentile that still lay within the threshold of observations. The variable was normally distributed after the adjustment was made.

As seen in Table 1 men averaged 6.00 drinks per week at baseline. The number of drinks per week increased at each time point with men reporting having 15.19 drinks per week at Wave 4. The average drinks per week in women also increased from baseline to Wave 4 (5.35 at baseline to 8.65 drinks per week at the Wave 4), though the change was smaller for women. Men reported slightly less than one episode of heavy drinking per month at the baseline, but the number of episodes increased for men to approximately 2.7 episodes per month at Wave 4. This increasing trend was also observed for women who reported slightly less than one heavy drinking episode a month at baseline to approximately 1.7 episodes a month at Wave 4.

Table 1

Alcohol Consumption Outcomes At Each Wave

	Baseline		10 Months		22 Months		46 Months	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Avg. Drinks Per Week								
Men	6	10.4	10.22	11.87	12.33	12.12	15.19	13.22
Women	5.35	8.29	7.57	7.85	8.2	8.29	8.65	7.02
Heavy Drinking Episodes								
Men	0.93	1.78	1.67	2.36	2.17	2.56	2.69	3
Women	0.89	1.87	1.14	1.76	1.45	2.07	1.72	2.4

As seen in Table 2, at every time point at least half the entire sample reported consequences of intoxication, such as experiencing hangovers, and waking in the morning to find they had forgotten part of the previous evening. At every time point over one-third of the entire sample reported feeling sick or throwing up after drinking, and saying things they later regretted. More than ten percent of the entire sample, at every time point, reported getting into a sexual situation they later regretted. Also, the percent of men in this sample who neglected to use birth control or protection from STD's was 7.95% at baseline, a rate that increased to 13.59% at Wave 4. Women reported a high of 7.26% in neglecting to use birth control or protection from STD's at Wave 3.

Table 2

Alcohol Consequences Outcomes At Each Wave

	Men				Women			
	Baseline	10 Months	22 Months	46 Months	Baseline	10 Months	22 Months	46 Months
Hangover in the morning after drinking.	51.97	60.95	64.55	67.96	53.33	59.75	67.74	72.35
Woke in the morning to find you had forgotten part of the evening before.	51.32	59.76	59.04	59.71	50.95	52.12	59.68	57.2
Felt sick or thrown up after drinking.	38.16	39.64	49.74	46.6	46.67	55.93	50.81	48.48
Said things you later regretted.	38.16	36.01	37.04	41.26	48.57	33.47	43.32	37.88
Gotten into a sexual situation you later regretted.	13.16	14.79	13.23	16.5	17.14	10.17	16.1	13.26
Neglected to use birth control or protection from STD.	7.95	7.69	9.04	13.59	5.76	3.39	7.26	6.44

Note. Percent of sample with problem at least once in the past 3 months.

Confirmatory Factor Analysis

Prior to investigating associations depicted in Figure 1, the measurement model for each endogenous latent variable underwent confirmatory factor analysis (CFA). The factor structures for each of the latent variables are shown in Figure 2 and results of CFA analyses on these constructs are described next.

It is recommended that the latent factors have no less than three indicators to properly specify the model and assure the structure is not under identified (Kline, 2005). Latent variables for Behavioral Undercontrol, Ethanol Sensitivity, Drinking

Motives, and Alcohol Expectancies included at least three indicators, as recommended (Kline, 2005). Fit indices, including the comparative fit index (CFI) and the standardized root mean square residual (SRMR), were evaluated to assess model fit. The CFI reflects the degree to which the sample variances and covariances are reproduced by the hypothesized model structure. CFI ranges from 0 to 1.0, with higher values, preferably greater than .90, reflecting better approximation of the data (Ullman, & Bentler, 2003). SRMR is a residual-based index. Specifically it is the standardized difference between the observed correlation and the predicted correlation. Lower values, preferably below .08, indicate a good model fit (Hu, & Bentler, 1998). Factor loadings were also examined in addition to overall fit indices to assess the adequacy of model specification. Factor loading estimates are given t-values and significance is calculated according to the t distribution.

Fit statistics for the measurement model of behavioral undercontrol could not be determined in confirmatory factor analysis. This was a result of the factor structure being “just-identified”, meaning that the number of parameters specified in the model equaled the number of estimable parameters in the variance-covariance matrix resulting in 0 degrees of freedom (Kline, 2005). A just identified model yields a trivially perfect fit making overall model fit statistics uninteresting (Rigdon, 1997). However, significant tests on the model’s pathways from the latent variable to the indicators (or loadings) can be calculated (Kline, 2005; Rigdon, 1997). Coefficients of the pathways from the individual items to the latent behavioral undercontrol variable ranged from .57 to .76 and were all significant at $p < .001$. In addition, earlier sections here reviewed each measure of behavioral undercontrol including impulsivity,

sensation seeking, and psychoticism and showed the theoretical support for these items' inclusion in the personality factor proposed in this study.

The factor labeled "subjective response" infers ethanol sensitivity – a self report (subjective) measure of an individual's response to the effects of alcohol. This factor includes the four individual items of the SRE scale, for the first five times one ever drank. The four item factor demonstrated good model fit ($CFI = .96$, $SRMR = .04$) with standardized factor loadings ranging from .71 to .95 (all p values were $< .001$)

The nine activity enhancement expectancy items (Kushner et al., 1994) were randomly parceled (Little, Cunningham, Shahar, & Widaman, 2002) into four groups, each with two items and one with three. The factor structure for activity enhancement expectancies and the items assigned to the different parcels as seen in Figure 2 demonstrated excellent model fit with $CFI = .99$ and $SRMR = .01$ along with significant loadings for all items ($p < .001$) ranging from .56 to .88.

Latent Growth Curve Models

Latent growth curve (LGC) modeling is used to capture growth in a construct over time using random coefficients that reflect initial status (intercept) and growth rate (slope). Following Bollen and Curran (2006) a two step approach was used to examine the trajectories of two different models, one model for heavy episodic drinking and the other model for alcohol consequences.

The LGC models for heavy episodic drinking and consequences in this study included data from all four assessments (baseline, 10 month follow up, 22 month follow up and 46 month follow up). Growth curve analyses were conducted using

Mplus 6.1 (Muthen & Muthen, 2010) on all available data using full-information maximum likelihood estimation for missing data (Arbuckle, 1996; Schafer & Graham, 2002).

Latent growth curve modeling began with estimation of unconditional models to determine the functional form of the slopes. Subsequently, conditional models were tested to analyze the impact of family history and OPRM1 on each outcome via the mediating variables previously described.

Examination of the conditional models' fit and support for the hypothesized sub-models include overall model fit indices (CFI, TLI, RMSEA, & SMR) (Bollen & Curran, 2006; Singer & Willett, 2003), and examination of the direct and indirect paths in the model. Hypothesized mediated relationships were tested following criteria detailed by MacKinnon (2008) by examining the indirect effects from family history and OPRM1 through the mediating variables. Robustness of the mediation models was investigated by comparing the two hypothesized fully mediated models to more saturated models of each outcome, resulting in four models being tested in our analyses. Results of these model tests are described the conditional model section below.

Unconditional Models

Initially, unconditional models (i.e., no covariates) for each outcome examined linear, non linear and quadratic slopes. Examination of plots for the estimated means and comparison of model fit statistics between varying functional forms of the data were used to determine the best descriptions of the models' trajectories. Piecewise (discontinuous) trajectories were not considered because piecewise trajectories are

inestimable with only four data points. Additional non-linear trajectories were examined with estimated time scores (Muthen, & Muthen, 2008).

The plot of the estimated means for heavy episodic drinking suggested a non linear trajectory and a non linear trajectory using estimated time scores was compared to a quadratic growth curve. The non linear trajectory resulted in acceptable fit indices for the model, but a quadratic trajectory resulted in much better explanation of the data (CFI = 1, RMSEA = 0 (0, .054), and SRMR = .001).

Examination of the estimated means for drinking consequences indicated that the slope was not strictly monotonic, however a linear trajectory was still tested because deviance in linearity appeared marginal. The linear trajectory resulted in acceptable model fit indices, however; substantial improvement resulted from the data being modeled with free estimates in the time scores (CFI = .99, RMSEA = .05 and SRMR = .03). Accordingly, based on these analyses, heavy episodic drinking was modeled as a quadratic function and alcohol consequences was modeled linearly with free estimates of time scores.

Conditional Models

Because the data for this study were part of a randomized controlled trial (Wood et al., 2010), all conditional models controlled for intervention effects by including intervention conditions as exogenous manifest variables with paths estimated to intercept, linear slope, and quadratic factors. Moreover, given observed gender differences in alcohol use and problems (Johnston et al., 2010; Substance Abuse and Mental Health Services Administration, 2009), conditional models also included gender as an exogenous manifest variable with paths estimated directly to the

intercept, slope and quadratic factors. The Brief Motivational Interviewing (BMI) treatment condition was the only intervention with direct associations on the exogenous factors and BMI was only directly related in the heavy episodic drinking model. An association of BMI was found on the linear and quadratic slope factors for heavy episodic drinking ($\beta = -.21$, $SE = .10$, $p < .05$, for the linear slope; $\beta = .25$, $SE = .12$, $p < .05$, for the quadratic slope) with a negative correlation between the linear and quadratic slopes ($r = -.95$, $p < .001$). This suggests that individuals who received the BMI intervention showed less growth in the linear slope of heavy episodic drinking from baseline to Wave 3, but more growth in the quadratic slope from Wave 3 to Wave 4 compared to all other conditions.

The direct associations of gender were positive on the slope of heavy episodic drinking, indicating that men had more of an increase compared to women in heavy drinking episodes ($\beta = .21$, $SE = .09$, $p < .05$). In the consequences model, gender was associated with the intercept of problems, such that men reported fewer consequences at baseline ($\beta = -.10$, $SE = .05$, $p < .05$) compared to women.

Comparisons of model fit indices for the hypothesized fully mediated models of heavy episodic drinking and consequences along with the fit indices of the saturated models of both outcomes are presented in Table 3. The fully mediated hypothesized models (consistent with Figure 1) were tested first for heavy episodic drinking. As can be seen in Table 3, this model showed good overall fit indices ($CFI = 0.92$; $TLI = 0.9$; $RMSEA = 0.058$; and $SRMR = .082$). For this model the R^2 values for the intercept, linear slope and quadratic factors were $.34$ ($p < .001$), $.013$ (ns), and $.10$ (ns) respectively.

Table 3

Fit Indices Of Conditional Latent Growth

Model	Chi-square (model <i>df</i>)	CFI	TLI	RMSEA	SRMR
HED					
Full Mediation	425.4 (158)	0.92	0.90	0.058	0.082
Saturated Model	375.8 (144)	0.93	0.91	0.056	0.071
Consequences					
Full Mediation	429.9 (165)	0.93	0.92	0.056	0.076
Saturated Model	393.2 (155)	0.94	0.92	0.055	0.071

Note. *DF* = degrees of freedom; *CFI* = comparative fit index; *TLI* = Tucker-Lewis index; *RMSEA* = root mean square error of approximation; *SRMR* = standardized root mean square residual;

As hypothesized, family history was positively related to personality, however, in contrast to our hypotheses family history was not related to subjective effects (see Figure 3). Also contrary to our hypotheses there was no association of OPRM1 with either personality or subjective effects and subjective effects were not related to expectancies and had no significant indirect associations between family history and heavy drinking.

Figure 3. Hypothesized Fully Mediated Heavy Episodic Drinking Model.

Figure 3. Dashed lines depict significant mediation paths.

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

Consistent with the enhanced reinforcement sub-model, tests of indirect effects on the mediating factors in the heavy episodic drinking model showed significant mediating effects from family history to the intercept of heavy drinking via behavioral undercontrol and alcohol expectancies ($\beta = .038$, $SE = .015$, $p < .05$). While significant positive associations were observed from expectancies to the slope of heavy drinking, indicative of a prospective effect, the indirect effect of family history (via behavioral undercontrol and alcohol expectancies) was not significant (see Figure 3).

To test the robustness of the hypothesized model for heavy episodic drinking a more saturated model was estimated to examine whether the observed associations would be retained and whether the fully mediated model is supported. The saturated model (Figure 4) includes direct paths from each exogenous factor to the intercept,

slope and quadratic factors along with direct paths from the mediating variables to the outcomes. For clarification, pathways proposed in the hypothesized fully mediated model were retained in the figure and new paths that were significant are also displayed. Departures and changes in the parameters from the hypothesized model are discussed.

Figure 4. Saturated Model of Heavy Episodic Drinking

Figure 4. Dashed lines depict significant mediation paths.
* $p < .05$; ** $p < .01$; *** $p \leq .001$.

The overall fit statistics for the saturated model improved slightly (CFI = .93; TLI = .91; RMSEA = .056; and SRMR = .071) (see Table 4). A Chi-square difference test comparing these two models indicated a significant increment in model fit for the more saturated model, $X^2 \Delta (14) = 49.6$, $p < .001$. R² values for the intercept, linear slope and quadratic slope factors were .40 ($p < .001$), .019 (ns), and .23 (ns) respectively. Given the incremental change in model fit, we elected to retain this

model and it is depicted in Figure 4. Direct effects from family history to the intercept, slope and quadratic factors were all non significant. Subjective effects were significantly and positively associated with the intercept and slope of heavy episodic drinking indicating that lower perceived responses to alcohol were associated with greater levels of initial heavy drinking and growth in this construct. In addition subjective effects demonstrated significant negative effects with the quadratic factor indicating that lower perceived responses were associated with a more modest decrease in heavy episodic drinking. The association from expectancies to the linear slope was not significant in the saturated model. Mediation of family history through behavioral undercontrol to the intercept was significant ($\beta = .027$, $SE = .014$, $p < .05$), as was the mediation from family history through behavioral undercontrol and expectancies to the intercept ($\beta = .028$, $SE = .012$, $p < .05$).

Model testing for alcohol consequences mirrored those presented for heavy episodic drinking, with the hypothesized full mediation tested first (Figure 5) followed by robustness testing using a more saturated model. Results of the fully mediated model for alcohol use consequences resulted in good overall fit indices ($CFI = .93$; $TLI = .92$; $RMSEA = .056$; $SRMR = .076$) (see Table 4). R^2 values for the intercept and linear slope factors were .30 ($p < .001$), and .22 ($p < .001$) respectively. Given that the exogenous and mediating factors are identical across the heavy episodic drinking and consequence models, these associations are depicted in Figure 5 but not discussed. As seen in Figure 5, the significance of the pathways is quite similar to the heavy episodic drinking model.

Figure 5. Hypothesized Fully Mediated Consequences Model.

Figure 5. Dashed lines depict significant mediation paths.
*** $p < .01$; *** $p \leq .001$.

As hypothesized, the mediating paths were significant from family history through personality and expectancies on both the intercept and slope ($\beta = .035$, $SE = .013$), $p < .01$, for the intercept; $\beta = .030$, $SE = .012$), $p < .05$, for the slope), however, in contrast to expectations, there was no significant mediation through subjective effects.

A more saturated model of consequences was also tested for comparison to the fully mediated model (see Figure 6).

Figure 6. Saturated Model of Consequences

Figure 6. Dashed lines depict significant mediation paths.
 $*p < .05$; $**p < .01$; $***p \leq .001$.

The saturated model for consequences also included direct paths from each exogenous factor to the intercept and linear slope factors along with direct paths from the mediating variables to the outcomes. For simplicity Figure 6 does not depict all the pathways that were tested. All existing paths from the fully mediated model are retained in the figure and only new paths that were significant are added to the figure. Changes from the fully mediated hypothesized model are discussed. The overall fit statistics for the saturated model improved (CFI = .94; TLI = .92; RMSEA = .055; and SRMR = .071) (Table 3). A Chi-square difference test comparing these two models indicated a significant increment in model fit for the more saturated model, $X^2 \Delta (10) = 36.7$, $p < .001$. R^2 values for the intercept and linear slope were .38 ($p < .001$), and

.28 ($p < .001$) respectively. Therefore this model was retained as the final model. Subjective effects were positively associated with the initial level of consequences, but negatively associated with the change in problems indicating that less sensitivity to alcohol was associated with less growth in problems over time.

There were no significant direct effects from family history on the intercept or slope; however, family history's influence on the intercept and slope of problems was mediated through both behavioral undercontrol and expectancies ($\beta = .024$, $SE = .010$, $p < .05$, for the intercept; $\beta = .029$, $SE = .012$, $p < .05$ for the slope). There was also mediation between family history and the intercept through behavioral undercontrol alone ($\beta = .034$, $SE = .015$, $p < .05$). Mediation of family history and the intercept and slope through expectancies alone was not significant.

CHAPTER 5

DISCUSSION

The major purpose of the present study was to examine a genetically-informed model of enhanced reinforcement in the prospective prediction of heavy drinking and alcohol problems in emerging adulthood. While the specified models provided very good fit to the data, overall support for hypothesized mediating pathways was mixed. Consistent with our predictions, we found that behavioral undercontrol/disinhibited personality traits and alcohol expectancies significantly mediated relations between a family history of alcoholism and both heavy drinking and alcohol problems. In contrast, we found no support for a hypothesized mediating role for behavioral undercontrol personality traits and subjective effects of alcohol in OPRM1 – alcohol outcome relations. Moreover, a hypothesized indirect effect between family history and alcohol outcomes via subjective effects of alcohol was also not observed.

We investigated the robustness of the enhanced reinforcement model by estimating additional paths from both exogenous (family history, OPRM1) and intervening (behavioral undercontrol, subjective effects) factors to alcohol outcomes. Based on significant increments in model fit, these more saturated models were retained as final models for both heavy episodic drinking (HED) and alcohol problems. The proposed mediation between family history – alcohol outcome relations were substantiated in the saturated models as shown in the results of the heavy episodic drinking outcome model and the consequences model. There were no

significant direct effects from family history on either of the alcohol outcomes. Mediation through both behavioral undercontrol and activity enhancement expectancies was significant on the initial levels of HED and consequences. This mediation was also significant on the linear slope of alcohol use consequences. A more direct mediation between family history and the intercept of both HED and consequences through behavioral undercontrol alone was significant in robustness testing of the more saturated models. However, observed prospective relations between expectancies and the linear slope in the HED model were not observed in the saturated model nor was the mediating role of personality and expectancies in family history – heavy drinking relations on the quadratic factor. Mediation between family history and alcohol outcomes through expectancies alone was also not significant. Next we elaborate on study findings and place them in the context of the larger theoretical model and prior research.

Toward a Model of Enhanced Reinforcement: Integrating Current Findings

Our findings that family history effects were indirectly associated with heavy drinking and alcohol problems via a behavioral undercontrolled/disinhibited personality traits and alcohol expectancies is consistent with the original enhanced reinforcement proposed by Sher (1991) as well as some subsequent cross sectional research testing the intervening influence of these factors between family history and alcohol problems (Finn, Sharkansky, Brandt, & Turcotte, 2000; Sher et al., 1991). These findings replicate and extend prior research, providing additional support of disinhibited personality traits (Caspi, Moffitt, Newman, & Silva, 1996; Rutledge & Sher, 2001; Schuckit & Gold, 1988; Schuckit et al., 1994; Schuckit & Smith, 2006a; Sher,

Bartholow, & Wood, 2000) and cognitions related to alcohol (Brown, Goldman, & Christiansen, 1985; Brown, Christiansen, & Goldman, 1987; Fromme, Stroot, & Kaplan, 1993; Fischer, Anderson, & Smith, 2004; Fischer, Settles, Collins, Gunn, & Smith, In Press; Kushner, Sher, Wood, & Wood, 1994) as important mechanisms by which family history risk influences heavy and problematic drinking in offspring. The observed indirect effects between family history and alcohol outcomes are noteworthy in that the current study did not utilize a high-risk design, oversampling on family history. Other research has also shown family history effects with alcohol problems via undercontrolled personality traits cross sectionally (Capone & Wood, 2008) and family history effects with heavy use via undercontrolled personality traits prospectively (Chassin, Flora, & King, 2004). Family history effects with heavy drinking via expectancies have been shown cross sectionally (LaBrie, Migliuri, Kenney, & Lac, 2010) and prospectively (Colder, Chassin, Stice, & Curran, 1997), also family history effects with problems via expectancies have been shown prospectively (LaBrie et al., 2010).

In contrast to our expectations, the integration of OPRM1, a candidate gene associated with the reinforcing effects of alcohol did not augment the prediction of heavy drinking and alcohol problems in our emerging adult sample. Hypothesized indirect associations were not observed in the initial model nor were direct effects obtained in the more saturated models. Difficulty replicating findings of associations between candidate genes and alcohol outcomes have been common, prompting some researchers to question the ultimate utility of the candidate gene approach (Risch et al., 2009). Nonetheless, the integration of candidate genes with replicated associations

with alcohol outcomes into longitudinal developmental studies has yielded new insights into transactional processes by which genes influence risk pathways during important developmental periods. For example, Dick et al. (2009) found support for the hypothesis that GABRA2, a candidate gene associated with alcohol dependence in the collaborative study of the genetics of alcoholism (COGA) and subsequent studies, would be associated with trajectories of externalizing behavior in early adolescence. Further, this effect was moderated by parental monitoring, such that genotype – externalizing behaviors were stronger when parental monitoring was low. Similar results were obtained for CHRM2, which had also been associated with alcohol dependence in the COGA project. Latendresse et al. (2011) observed associations between CHRM2 and externalizing behaviors, which were moderated by peer group antisocial behavior; CHRM2 – externalizing behavior relations were stronger among those exposed to higher levels of peer antisocial behavior. Others (Ray, & Hutchison, 2004; van der Zwaluw, Kuntshe, & Engels, 2011) have argued in support of the candidate gene approach as one of the important ways in which genetic influences on alcohol outcomes are elucidated. Though comparison across studies is complicated by an array of factors such as the heterogeneity of the phenotypes of alcohol use and misuse, sample differences (e.g., clinical vs. population), Type I errors associated with multiple comparisons, and study designs (Dick, Latendresse, & Riley, 2011). The inconsistent patterns of association that have characterized the candidate gene approach more generally have been observed specifically with respect to OPRM1. Yet evidence of OPRM1 – alcohol outcomes has been shown. The G allele in the A118G SNP of the OPRM1 gene has been shown to relate with relatively strong appetitive

tendencies and craving toward alcohol (Wiers et al., 2009; van den Wildenberg et al., 2007). Associations between multiple polymorphisms of the OPRM1 gene have been found with subjective responses to alcohol including effects such as dizziness, clumsiness, drunkenness, nausea, etc. (Ehlers, Lind, & Wilhelmsen, 2008; Ray, & Hutchison, 2004). OPRM1 has also been associated with alcohol dependence (Koller et al., 2012; Kranzler, et al., 1998; Luo, Kranzler, Zhao, & Gelertner, 2003; Zhang, et al., 2006). Consistent with the current findings several researchers have not been able to successfully replicate OPRM1's association on alcohol dependence (Arias, Feinn, & Kranzler, 2005; van der Zwaluw et al., 2007).

Contrary to hypotheses the Self-Rating of the Effects of Alcohol (SRE) had no impact as a mediating factor in the enhanced reinforcement model and was not related to either family history of alcoholism or OPRM1. These results are contrary to findings from Shuckit, & Smith (2006b) that showed level of response, as measured by the SRE, mediated relations between family history of alcoholism, heavy drinking and problems. Shuckit and Smith's model was a high risk design sampling specifically for children of alcoholics. It also predicted SRE's effects on alcohol outcomes through disinhibited personality characteristics and alcohol expectancies. In addition results from other studies have shown that the SRE mediated family history effects on heavy drinking and problems through expectancies alone (Shuckit et al., 2005; Schuckit, Smith, Trim, Kiekebaum, Hinga, & Allen, 2008). While results of this study did not affirm the indirect effect of the SRE on heavy drinking or alcohol use problems, results from the saturated model did indicate significant direct effects of the SRE on both alcohol use outcomes. A decreased sensitivity to the effects of alcohol was

positively associated with initial levels of heavy drinking, along with the increase in the linear slope of heavy drinking, but was negatively associated with the down turn of the quadratic slope of heavy drinking. These results indicate that individuals with a lower sensitivity to the effects of alcohol engaged in greater heavy drinking compared to others. The SRE was also positively associated with the initial levels of alcohol problems and negatively associated with problems over time indicating that individuals with lower sensitivity to alcohol may experience fewer problems associated with alcohol use over time. The findings for SRE's direct effects in this model are consistent with previous work (Schuckit et al., 2008a; Schuckit et al., 2008b; Schuckit et al., 2009; Schuckit, 2009; Volavka et al., 1996). Prospective analysis has shown SRE to be influential on alcohol use and problems (Schuckit et al., 2008b; Schuckit et al., 2007), however in one study SRE effects on maximum drinks went away after controlling for baseline maximum drinking (Schuckit et al., 2008b) and in the other study baseline drinks were not controlled for (Schuckit et al., 2007). Baseline drinking was controlled for in this study, so prospective results of this study showing SRE's effect on alcohol misuse and problems helps contribute to the body of research showing SRE's influence on alcohol use outcomes.

Strengths and Limitations.

The lack of ethanol sensitivity's involvement in the model as hypothesized might relate to the way this factor was measured in our study. Ethanol sensitivity was not measured consistent with its explanation in Sher's original model. The SRE scale used here purportedly measures innate tolerance more than sensitivity. Other measures of sensitivity may be more appropriate. For example, in his model Sher states that

“decreased sensitivity on the descending limb of the BAC can easily be accommodated to the model (to measure ethanol sensitivity)” (p. 135, 1991). A measure that captures biphasic responses to alcohol, such as the Biphasic Alcohol Effects Scale (Martin, Earleywine, Musty, Perrine & Swift, 1993) would be better suited for analyzing sensitivity to alcohol, especially because the ascending phase relates to the stimulation and euphoric effects of alcohol. It is sensitivity to the euphoric effects of alcohol that is purported to influence alcohol misuse in the enhanced reinforcement model. Corroboration of the enhanced reinforcement model including a more specific measure of ethanol sensitivity is needed, however these results are important as they offer longitudinal support of the SRE which has primarily undergone cross sectional analysis.

The enhanced reinforcement model does not include environmental factors and does not account for how these factors influence individual susceptibility to alcohol misuse. Sher’s 1991 heuristic, overarching model, accounts for environmental factors such as life stress, parenting behavior and peer influences. These influences cannot be overlooked and need to be included when assessing vulnerability, however the enhanced reinforcement model tested here serves as an initial analysis elucidating influences of multiple trajectories proposed by Sher. Additional analysis can, and should, be done with environmental considerations included.

This study was a post hoc analysis of data collected as part of an intervention study conducted with college students and was not designed to specifically measure the enhanced reinforcement model. The post hoc design may raise issues of generalizability, particularly given that the sample was comprised of an ethnically

homogenous population drawn from a single campus at a public, northeastern university. As noted, the use of the SRE to measure ethanol sensitivity and the lack of a high-risk family design are further limitations.

Despite these limitations, the current research replicates and extends prior research in multiple ways, notably with respect to the ability to conduct a fairly comprehensive test of an influential etiologic model with a large prospective sample of emerging adults.

Conclusion

The inclusion of a candidate gene associated with alcohol's reinforcing effects was not supported and, as noted, support for the integration of the candidate gene approach into etiologic models has been modest. Commenting on this issue, Dick et al. contend that the incorporation of genetics into longitudinal developmental research has great potential for furthering current understanding of the mechanisms by which genetic susceptibility may or may not influence the development of risk behaviors such as alcohol misuse. Nonetheless, they caution that given the rapidly evolving state of genetic research, important design considerations (e.g., candidate gene vs. genome wide associations vs. sequencing), and unique considerations in the analysis of genetic data, close collaboration between geneticists and social scientists are necessary to achieve meaningful advances. Genetic studies have the capability of doing much more than simply looking at single indicators of risk or susceptibility. Results of this study do not support OPRM1's singular influence on the vulnerability toward alcohol misuse and it may not be adequate to single out OPRM1 as a major individual contributor to alcohol misuse. Rather; it may be better to examine OPRM1 within a

candidate systems approach, in which multiple single-nucleotide polymorphisms with functional relevance are aggregated to form a composite genetic risk score that may better explain alcohol outcomes (Derringer et al., 2010).

Despite the noted limitations, the current results contribute to understanding the psychosocial correlates of heavy drinking and alcohol problems among a developmentally at-risk population, emerging adults. Support for elements of the enhanced reinforcement model such as the mediating role of personality and alcohol expectancies in family history alcohol outcome relations extends prior research as do the observed prospective associations between subjective effects of alcohol and heavy drinking and alcohol problems. Aside from their etiologic significance, these findings may further inform the development of more tailored preventive interventions that specifically target etiologically relevant factors such as subjective response to alcohol (Schuckit et al., in press) or personality (Conrod, Castellanos-Ryan, & Strang, 2010).

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