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ALCOHOL-INDUCED BLACKOUTS: LESSONS LEARNED FROM EXAMINING THREE RISK FACTORS

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ALCOHOL-INDUCED BLACKOUTS:
LESSONS LEARNED FROM EXAMINING THREE RISK FACTORS

by

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Dedication

For Mom and Dad, my biggest supporters

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ALCOHOL-INDUCED BLACKOUTS: LESSONS LEARNED FROM EXAMINING THREE RISK FACTORS

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Alcohol-induced blackouts, one neurobiological consequence of alcohol use, are periods of amnesia for all or part of a drinking event. Risk factors for blackouts include a family history of problematic alcohol use (FH+), early onset of drinking, and subjective responses to alcohol. The objective of this project was to examine how these factors confer risk for blackouts, as well as to what extent blackouts predict a motivation to decrease drinking. Participants were from a 6-year, longitudinal study of first time college students. Self-reported frequency of blackouts, motivation to change drinking behavior, indices of alcohol consumption, and subjective intoxication (i.e., feeling drunk) were assessed annually during Years 4-6. Age at drinking onset (i.e., age at first drink, first high, and first drunk) was assessed at Year 4. FH+, captured at baseline, was coded if participants self-reported that their mother, father, or any of their four grandparents were a possible or definite problem drinker. Overall, 52% to 69% of participants reported experiencing blackouts during Years 4-6. With respect to FH+, women were more likely to report blackouts than men; however, compared with women with a maternal FH+, men with a maternal FH+ were more than twice as likely to report blackouts. Additionally, after controlling for year specific binge drinking, a growth curve model indicated that early onset drinkers reported more frequent blackouts at Year 4. There were, however, no significant

effects of acceleration or deceleration in the frequency of blackouts across the three years. Early onset drinkers continued to experience more frequent blackouts compared with those who initiated alcohol use later, despite decreases in binge drinking over time. Finally, in a cross-lagged model, subjective intoxication (i.e., feeling drunk) prospectively predicted experiencing blackouts. Controlling for both objective (e.g., quantity) and subjective intoxication, blackouts at Year 4 predicted greater motivation to change drinking behavior at Year 5, but this motivation did not predict less quantity of alcohol use by Year 6. Altogether, early onset drinking, maternal FH+, and subjective intoxication are robust predictors of blackouts. The underlying mechanisms behind these markers of risk involve both environmental and genetic factors, which likely operate together.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

Emerging adulthood (ages 18 to 29) represents a unique developmental period (Arnett, 2000; Arnett, Žukauskienė, & Sugimura, 2014) in which individuals begin to accept responsibility for themselves (Arnett, 2001, 2003) and a period when they are afforded unrestricted exploration in self-identity (e.g., worldviews, love, work). Behavioral risk-taking also peaks during this period (Arnett, 2000), including alcohol use (Substance Abuse and Mental Health Services Administration, 2017). Although this experimentation with alcohol is common, it is important to note that individuals respond differently to the intoxicating effects of alcohol, with effects ranging from subjective feelings of stimulation or sedation to observable changes in behavior and even alterations in certain neural functions. One of the more significant and intriguing neurobiological effects of alcohol is its ability to affect the functioning of the hippocampus and associated brain regions (White, Matthews, & Best, 2000b), which results in deficits in memory processing and ultimately an alcohol-induced blackout.

Phenomenology of Alcohol-Induced Blackouts

Alcohol-induced blackouts are periods of partial or total anterograde amnesia for all or some of the events taking place during a drinking episode (Hartzler & Fromme, 2003b; Wetherill & Fromme, 2011; White, 2003). Individuals who experience blackouts are unable to recall events, conversations, or even their own actions that occurred during the blackout. Individuals in a blackout may appear to be functioning normally to observers due to the fact that other cognitive and physical functions remain intact (Goodwin, 1995; Jennison & Johnson, 1994). Although they are still functioning, their brains are not recording the memories of their actions and experiences (White, 2003). This is because alcohol impairs the brain's ability to transfer new information from short-term into long-

term memory (see Figure 1) (White, 2003). Thus, individuals in a blackout have difficulty remembering their actions and experiences during the drinking event because their brains never recorded those episodic memories (White, 2003).

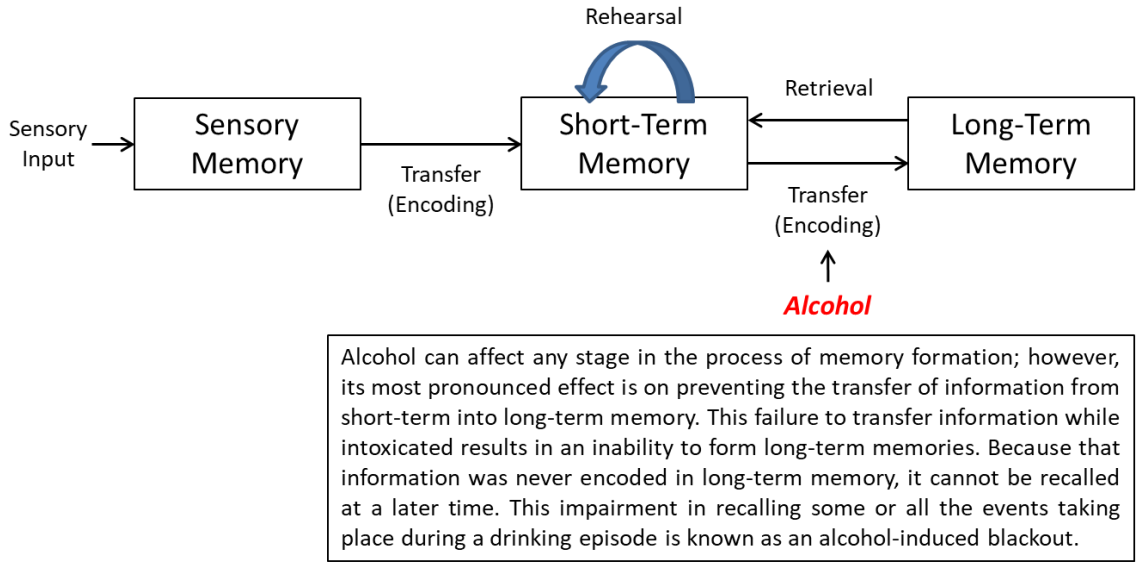

Figure 1. Demonstrating alcohol's primary effect on memory processing, adapted from White (2003)

Because memory encoding and storage is a complex process, many brain regions are involved (see Figure 2). The frontal lobes, including the lateral prefrontal cortex, are used in episodic encoding, which is a process by which the brain connects facts to the situation in which they were initially learned (Blumenfeld & Ranganath, 2007). Consuming alcohol, a neurotoxic agent, can interfere with memory encoding and storage by altering the functioning of neural structures involved in memory processing. Early work found that among moderate social drinkers (consuming < 15 drinks per week), alcohol intoxication detrimentally affected the prefrontal and temporal lobes, which impaired memory processing (Peterson, Rothfleisch, Zelazo, & Pihl, 1990). This suggests that blackouts may

be a result of alcohol differentially affecting brain regions involved in memory functioning. Indeed, dispelling the original idea that alcohol causes global depression of the central nervous system, scientific advances in the way researchers analyze how the brain functions have led to the belief that alcohol-induced blackouts are due to alcohol specifically disrupting how the hippocampus and associated brain regions function (White et al., 2000b).

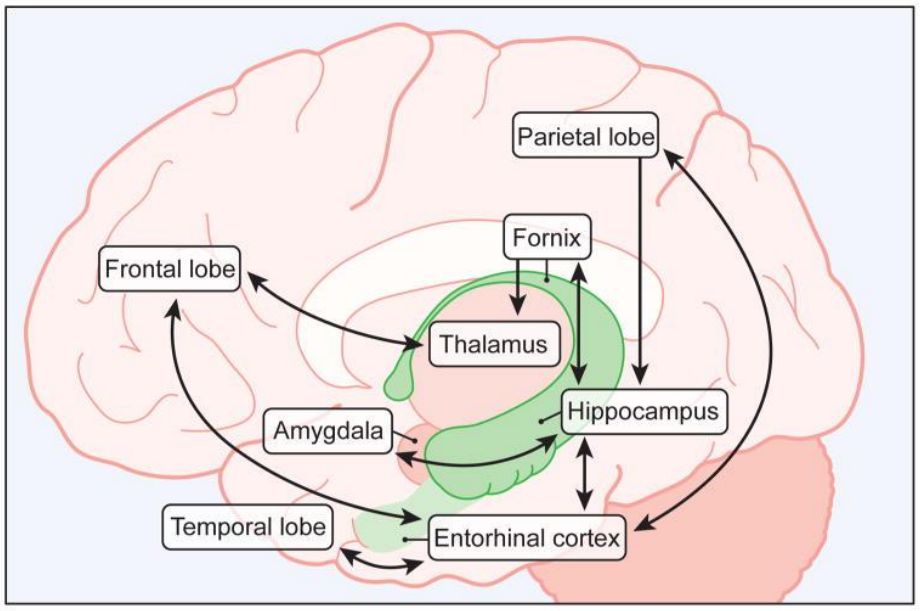

Figure 2: Primary brain structures involved in memory, reproduced from Wetherill and Fromme (2016) with permission from John Wiley and Sons

As such, another brain structure involved in the formation and storage of memories is the hippocampus (Burgess, Maguire, & O'Keefe, 2002), which is thought to be essential in the process of transferring information from short-term into long-term memory. Alcohol interrupting the transfer of new information from short-term into long-term memory could, in turn disrupt how the hippocampus processes memories for later retrieval (White, 2003). In fact, the hippocampus is especially sensitive to the effects of alcohol, such that alcohol

has been shown to prevent memory formation by altering normal hippocampal functioning (White et al., 2000b). This indicates that the hippocampus plays a key role in memory functioning. Because alcohol downregulates the hippocampus, this, in turn can increase the likelihood of experiencing alcohol-induced blackouts.

In line with this notion, recent evidence suggests that alcohol-related decline in gray matter volume in the hippocampus and para-hippocampus measured using magnetic resonance imaging was associated with those emerging adults reporting blackouts (Meda et al., 2018). Additionally, others have used proton magnetic resonance spectroscopy to measure glutathione concentration, the primary antioxidant found in the brain that can prevent damage resulting from oxidative stress, among individuals with bipolar disorder and controls (Chitty, Lagopoulos, Hickie, & Hermens, 2014). They found that among both groups of emerging adults, reduced glutathione in the hippocampus was associated with the occurrence of blackouts. These recent studies bolster prior work suggesting that the hippocampus plays a key role in alcohol-induced blackouts. Yet, the hippocampus is not the only brain structure involved in memory processing.

In fact, evidence for the role of additional neural regions exists with several studies examining the neural substrates of blackouts from adolescence through emerging adulthood. Some have assessed adolescents prior to their initiation of alcohol use and then followed them longitudinally (Wetherill, Castro, Squeglia, & Tapert, 2013). The authors found greater activation in frontal and cerebellar brain regions during a task of inhibitory control among substance naïve adolescents who would later progress to heavy drinking and experience blackouts compared with adolescents who would progress to heavy drinking but not experience blackouts and compared with those who remained substance naïve. Because these differences in neural activation manifested prior to alcohol use initiation, there is likely an underlying susceptibility towards experiencing blackouts. This

suggests that factors other than just amount of alcohol being consumed are involved in the occurrence of these phenomena.

Among emerging adults, findings are consistent with altered neural functioning and activation among those reporting blackouts. Researchers have compared individuals with a history of blackouts with those without a history of blackouts to examine whether this history affects future indices of altered neural functioning and activation. They found that there were no differences in episodic or contextual memory when sober; however, after low-dose alcohol administration with a maximum target BAC of .08g%, those who reported experiencing blackouts demonstrated impaired episodic or contextual memory (Hartzler & Fromme, 2003b; Wetherill & Fromme, 2011). In a follow-up study using fMRI, those with a history of blackouts had difficulties recalling spatio-temporal and social context of events and showed reduced patterns of brain activation in prefrontal and parietal regions of the brain (Wetherill, Schnyer, & Fromme, 2012). Because consuming alcohol differentially affects neural activation and functioning among those reporting a history of blackouts versus those without such a history, experiencing blackouts has lasting effects in altering neural functioning during subsequent drinking episodes. Thus, having a history of blackouts may be a risk factor for experiencing blackouts in the future.

Additionally, magnetic resonance spectroscopy found that emerging adults who binge drank and who also experienced blackouts showed alterations in the neurochemistry in their anterior cingulate cortex, exhibiting lower gamma amino-butyric acid (GABA) and glutamate levels (Silveri et al., 2014). Alcohol also affects neurochemistry in other brain regions. In the hippocampus, alcohol alters GABA neurotransmission (Leonard, Gerak, Delatte, Moerschbaecher, & Winsauer, 2009; Rabinowitz, Cohen, Finn, & Stackman, 2014), as well as N-methyl-D-aspartate (NMDA) and glutamate neurotransmission, which affects memory functioning, including learning and memory consolidation (Lovinger,

White, & Weight, 1990). In fact, animal models have long since demonstrated alcohol's effects in altering the neurotransmission of GABA and NMDA (Criswell et al., 1993; Givens & Breese, 1990; Simson, Criswell, & Breese, 1993). Because GABA, NMDA, and glutamate are involved in memory processing, alcohol's effect in altering the functioning of these genes may be one mechanism underlying the manifestation of blackouts. Overall, the neurotoxic effects of alcohol detrimentally affect the functioning and neurochemistry of certain regions of the brain involved in memory processing, highlighting the fact that blackouts are unique and intriguing neurobiological phenomena.

Contrary to popular belief, blackouts do not represent a loss of consciousness but rather reflect that failure to form long-term memories. In fact, individuals in a blackout have been known to engage in complex and often emotional and salient activities, such as engaging in unprotected intercourse with both acquaintances and strangers, driving an automobile, vandalizing property, and getting into arguments and physical altercations (Buelow & Koeppel, 1995; White, Jamieson-Drake, & Swartzwelder, 2002; White, Signer, Kraus, & Swartzwelder, 2004). As such, blackouts are associated with various dimensions of behavioral risk-taking. With this, an individual who is in a blackout may pose a significant danger to himself/herself and others.

IMPORTANCE OF STUDYING BLACKOUTS

The immense psychological and physical magnitude of blackouts necessitates furthering our understanding of these phenomena. Indeed, some individuals have described their blackouts as frightening (White et al., 2004) and emotionally stressful (Buelow & Koeppel, 1995). Additionally, blackouts are prospectively associated with risk for experiencing other alcohol-related consequences. For instance, individuals with a history of blackouts are more likely to experience future alcohol-related injuries (Hingson, Zha,

Simons-Morton, & White, 2016; Mundt, Zakletskaia, Brown, & Fleming, 2012), future social and emotional consequences (Wilhite & Fromme, 2015), as well as myriad other consequences, including overdosing on alcohol, engaging in illegal activities (e.g., damaging property), legal trouble, hangovers, and school or work problems (Hingson et al., 2016). Moreover, others have found that a pattern of blackout drinking prospectively predicted incapacitated sexual revictimization among women with a history of adolescent sexual victimization (Valenstein-Mah, Larimer, Zoellner, & Kaysen, 2015). Altogether, this body of evidence suggests that blackouts are not only problematic, but they are also dangerous. Given the high personal, societal, and health care costs of blackouts, some have emphasized the need for prevention efforts aimed at reducing blackouts (Mundt & Zakletskaia, 2012).

BLACKOUTS AND MOTIVATION TO CHANGE DRINKING BEHAVIOR

In addition to the dangers associated with blacking out, experiencing frequent blackouts can become distressing and problematic for affected drinkers (Buelow & Koeppel, 1995; White et al., 2004). With a negative subjective interpretation of blacking out, some drinkers were motivated to monitor their drinking for weeks after experiencing a blackout (White et al., 2004). This suggests that blackouts may be associated with an intrinsic recognition that their drinking was problematic and changing this pattern of drinking may be necessary to avoid blacking out. This recognition may encourage some drinkers to express a motivation to change their drinking behavior; however, this association has yet to be examined.

Altogether, blackouts are not only indicators of a pattern of potentially problematic drinking, but they also serve as potent risk factors for other significant, alcohol-related consequences in the future. With a negative subjective interpretation of blacking out and/or

experiencing significant associated consequences, some drinkers may then be motivated to change their drinking habits to avoid blacking out. Making behavioral changes is likely to be initiated by recognition of a problem (e.g., interpreting frequent blackouts as problematic) and, importantly, then being motivated to change the behavior that is leading to the problem. This indicates that understanding the underlying phenomenology of blackouts is crucial.

EARLY RESEARCH IN BLACKOUTS

Two early studies that were particularly influential in beginning to understand these phenomena described two types of blackouts: fragmentary and en bloc (Goodwin et al., 1969a; Goodwin, Crane, & Guze, 1969b). Partial alcohol-induced amnesia represents a fragmentary blackout, whereas total alcohol-induced amnesia represents an en bloc blackout. During fragmentary blackouts, the brain records pieces of memories, but alcohol prevents the brain from forming complete memories, leading to partial amnesia for the events taking place during that drinking episode. As a result, individuals who experienced a fragmentary blackout can recall some but not all the events that took place during the blackout. This is oftentimes accomplished using recall cues, such as pictures or recollections from others that were present during the blackout. In an en bloc blackout, individuals cannot recall any of the events that took place during the blackout, even when presented with recall cues. Indeed, it is not possible to retrieve memories or even pieces of memories that were never formed or encoded in long-term memory. Estimates indicate that fragmentary blackouts occur up to three times as often as en bloc blackouts (Anthenelli et al., 1994; Hartzler & Fromme, 2003a; Jennison & Johnson, 1994; Rose & Grant, 2010; White et al., 2004).

Early work in blackouts utilized high-dose alcohol administration to experimentally induce a blackout. For example, Ryback (1970) induced blackouts by asking seven alcoholic participants to consume alcohol in a hospital ward over the course of several days. Some participants' blood alcohol concentrations (BACs) reached levels of over .30g%. At that level of intoxication, most participants experienced a blackout, which was established by interviewing participants about their recollection of their own behavior witnessed by a research staff member. In another study, alcoholic subjects completed a 10-day period of sobriety, after which they were given free access to 100-proof alcohol for 12-14 consecutive days, with a maximum allowable consumption of one quart of alcohol per drinking day (Tamerin, Weiner, Poppen, Steinglass, & Mendelson, 1971). Six of 13 participants experienced a blackout, with blackouts being more prevalent in those with short-term memory impairments. Tamerin and colleagues (1971) also concluded that greater levels of intoxication produced greater memory impairments, finding that blackouts were more related to blood alcohol level than to the duration of the drinking episode. Others have dosed participants to BACs as high as .228g%, at which point eight out of 10 participants experienced a blackout (Miller, Hertel, Saucedo, & Hester, 1994). Miller and colleagues (1994) also found self-reported intoxication to be positively related to an individual's degree of memory impairment the following day.

In total, this early work demonstrated that alcohol impairs memory, especially at high doses, with progressive memory impairments at increasing levels of intoxication. Thus, blackouts were identified as a pharmacologic effect of alcohol consumption. In at least three studies, researchers also concluded that experiencing blackouts served as a risk factor for experiencing future blackouts (Goodwin et al., 1970; Miller et al., 1994; Tamerin et al., 1971).

During this early work, blackouts were thought to be a symptom of alcohol dependence due to their high prevalence in alcoholics, the first population to be studied regarding the occurrence of blackouts (Goodwin, Crane, & Guze, 1969a; Jellinek, 1952). In fact, Jellinek (1952) suggested that blackouts represented one of the foremost prodromal symptoms of later developing alcohol dependence. In comparison to Jellinek (1952), later researchers proposed that blackouts suggested a latter manifestation of alcoholism rather than a prodromal symptom (Goodwin et al., 1969a). Despite the difference in opinion, the notion that blackouts constituted symptoms of alcohol use disorder persisted for many years; however, more recent research has since refuted this idea (Anthenelli et al., 1994; Wilhite & Fromme, 2015).

A Resurgence in Research in Blackouts

Although blackouts are indicators of problematic drinking, the extant literature in blackouts is limited in comparison to what we know about other significant negative consequences of alcohol consumption. This is interesting as blackouts emerged in the literature 70 years ago; however, there was an extended period when blackouts were not studied. The large gap in research is because some researchers initially studied blackouts in the laboratory where they gave participants doses of alcohol that would be sufficient to produce a blackout. When researchers were no longer ethically able to dose participants to such high BACs, blackouts were largely neglected. The resurgence of blackouts in the literature occurred when researchers began assessing blackouts by retrospective self-report, as well as experimental studies comparing those who blackout with those who do not in low-dose alcohol administration studies. Currently, self-report is the method by which blackouts are measured.

Using self-report and low-dose alcohol administration with a maximum target BAC of .08g%, recent studies have demonstrated that individuals with a history of blackouts compared with those without such a history, show impaired episodic or contextual memory when intoxicated (Hartzler & Fromme, 2003; Wetherill & Fromme, 2011). They also demonstrate alterations in neural activation (Wetherill et al., 2012). Even without experimentally inducing a blackout, this recent evidence suggests that blackouts are, indeed, significant neurobiological consequences of alcohol consumption.

In dispelling the originally proposed idea that blackouts were symptoms of alcohol use disorder, research that is more recent has found that blackouts are common phenomena in otherwise healthy drinkers. Estimates indicate that about half of drinkers experience blackouts (Barnett et al., 2014; White et al., 2002). Yet, this finding should be taken into the context that some drinkers experience blackouts whereas others do not despite consuming alcohol to similar levels of intoxication. Altogether, both the early work and this recent work documented this differential susceptibility to experiencing blackouts, suggesting that risk for blackouts involves factors, other than just BAC, that are influenced by numerous environmental and genetic mechanisms.

RISK FACTORS FOR BLACKOUTS

Generally, blackouts occur with excessive alcohol intake that produces high BACs (Perry et al., 2006). In fact, it was originally proposed that alcohol's effect in creating blackouts is dose-dependent (Ryback, 1971), with noticeable impairments in memory starting at BACs of .14g% and higher (White, 2003). Blackouts have, however, also been reported at BACs as low as .07g% (Hartzler & Fromme, 2003a).

Although BAC as a risk factor for blackouts has been widely studied across the years, other individual risk factors have not garnered the same amount of attention. This is

interesting because we know that not all individuals who drink to a high BAC will experience blackouts, and thus, other factors must be involved. Two examples of other factors that place drinkers at risk of experiencing blackouts after controlling for current alcohol consumption include being female (White et al., 2002) and being Caucasian (Jennison & Johnson, 1994). In order to broaden our knowledge of the different individual risk factors for blackouts, research should focus on emerging adults, as emerging adulthood represents a key developmental period marked by increased personal freedom and experimentation with alcohol (Arnett, 2000).

One prime example of this includes investigating three individual factors that generate risk for alcohol-induced blackouts across this developmental period. These risk factors for blackouts are a family history of problematic alcohol use (FH+) (Jennison & Johnson, 1994; LaBrie, Hummer, Kenney, Lac, & Pedersen, 2011), an early onset of drinking (Jennison & Johnson, 1994; White et al., 2002), and subjective responses to alcohol (Schuckit, Smith, Goncalves, & Anthenelli, 2016a; Wetherill & Fromme, 2009).

Risk for Blackouts Across Emerging Adulthood

Evidence indicates that individuals who had exposure to alcoholic relatives growing up were more likely to report experiencing blackouts (Jennison & Johnson, 1994; LaBrie et al., 2011). LaBrie and colleagues (2011) found that those with a FH+ were also more likely to report blackouts during a drinking episode in which they engaged in preparty drinking compared with FH- individuals. Further, Jennison and Johnson (1994) found that FH+ individuals were more likely to continue experiencing multiple blackouts across time (i.e., blackout chronicity). In fact, the authors found that having three or more alcoholic or problem drinkers in the family was the strongest predictor of blackout chronicity.

The timing of initiation of alcohol consumption is also important as initiating alcohol use at an early age is also a risk factor for experiencing blackouts (Jennison & Johnson, 1994; White et al., 2002). White and colleagues (2002) found that an early onset of drinking, defined as initiating alcohol use at age 16 or younger, was associated with ever experiencing a blackout, having blacked out in the past year, and reporting 3 or more blackouts. Similarly, Jennison and Johnson (1994) found that initiating alcohol use at an early age was associated not only with blacking out, but with blackout chronicity as well. Chronicity of blackouts was also more likely among early onset drinkers who engaged in heavy drinking (i.e., drinking 5 or more drinks per drinking occasion on 4-8 or more days in the past 30 days).

After initiation of alcohol use, a third risk factor for blackouts is individual differences in subjective responses to alcohol. Some have found that a low level of response to alcohol (e.g., needing more drinks to feel the effects during the first 5 times ever drinking) was associated with experiencing blackouts (Schuckit, et al., 2016a). Further, feeling greater stimulating and sedative effects of alcohol during a heavy drinking occasion (i.e., 21st birthday celebration) was associated with reporting having blacked out during that drinking episode (Wetherill & Fromme, 2009). Whereas this evidence demonstrates that these subjective responses to alcohol are associated with blackouts, less is known about subjective feelings of intoxication (e.g., feeling drunk). Although subjective intoxication is another response to alcohol that likely also confers risk for blackouts, research has largely focused on subjective feelings of sedation or stimulation. Thus, examining additional indices of subjective responses to alcohol is useful to further understand the myriad factors that place drinkers at risk for experiencing these significant, negative consequences of alcohol consumption.

Despite the inherent connection with one another, these three risk factors have received minimal attention. In contrast to the risk factors associated with BAC, drinkers may have less control over these individual risk factors. This would suggest that inherent qualities, such as having a FH+, having already initiated alcohol use at an early age, and being sensitive to subjective responses to alcohol, are likely operating through both environmental and genetic pathways to generate risk for experiencing alcohol-induced blackouts.

Environmental Risk for Blackouts

In a FH+ household, parents may model drinking in front of children, thus producing a type of high-risk environment in which drinking, and perhaps problematic drinking, can appear to be normative. Children may also have easy access to alcohol in these households due to parents' lax views regarding alcohol use and low parental monitoring, which may promote an environment in which alcohol use by children is acceptable. Because parents have greater influence over their children when the children are younger (Dick, 2011), environmental factors stemming from growing up in a FH+ household can influence when individuals will initiate alcohol use and to what extent they will engage in problematic drinking. In fact, Dick (2011) found that children who grow up in a FH+ household often initiate alcohol use at an early age.

After initiation of alcohol consumption, FH+ individuals are at increased risk for developing problematic drinking patterns and for experiencing alcohol-related consequences (LaBrie, Migliuri, Kenney, & Lac, 2010; Sørensen et al., 2011). Specifically, LaBrie and colleagues (2010) found that FH+ individuals were more likely to black out on a prepartying night (i.e., when they consume alcohol prior to going to a bar or party where they plan to consume more alcohol) compared with FH- individuals who also engaged in

prepartying. This suggests that associating with a deviant peer group that encourages this type of heavy drinking may put FH+ individuals at greater risk for experiencing blackouts compared with their FH- counterparts.

Because peers begin to have more influence than parents during adolescence (Dick, 2011), adolescents may develop problematic drinking behaviors by associating with deviant peers who encourage alcohol use (Trucco, Colder, Wieczorek, Lengua, & Hawk, 2014). After this initiation of alcohol use at an early age, those adolescents then have more time to develop problematic drinking patterns by the time they reach emerging adulthood. This can influence whether early onset drinkers will develop problematic drinking styles that ultimately result in alcohol-related consequences (McCambridge, McAlaney, & Rowe, 2011), including blackouts.

Specifically, risk for experiencing blackouts is associated with styles of heavy drinking. Merrill and Read (2010) found drinking to increase positive affect to be directly associated with blackouts. Others have found drinking for the purpose of getting drunk to be associated with a greater likelihood of blacking out (Boekeloo, Novik, & Bush, 2011). Another salient risk factor among emerging adults is playing drinking games (LaBrie et al., 2011; Ray, Stapleton, Turrisi, & Mun, 2014; Wahl, Sonntag, Roehrig, Kriston, & Berner, 2012). Because drinking games typically involve drinking heavily over a short period of time, this popular form of alcohol consumption among emerging adults can put them at increased risk for many other alcohol-related consequences, including alcohol poisoning, alcohol-related injuries, experiencing unwanted sexual contact, as well as social, emotional, and health problems (Barbieri et al., 2015; Grossbard, Geisner, Neighbors, Kilmer, & Larimer, 2007; Johnson & Stahl, 2004). In total, environmental factors involving parents and peers can promote early initiation of alcohol use, which gives early onset drinkers more time to then develop problematic drinking styles that are

indicative of patterns of heavy drinking that will increase the likelihood that those individuals will experience blackouts during emerging adulthood.

One result of initiating alcohol use at an early age is that it can influence how early onset drinkers respond to the intoxicating effects of alcohol later in life (Israel, Quintanilla, Karahanian, Rivera-Meza, & Herrera-Marschitz, 2015). Thus, individuals who initiated alcohol use at an early age may be more sensitive to subjective feelings of intoxication by the time they reach emerging adulthood. With this, high-risk environments that involve engaging in heavy drinking can influence the extent to which these individuals will choose to drink to intoxication (Link, 2008; Teunissen et al., 2016).

Emerging adults often seek social acceptance, and heavy alcohol use represents a primary means of socializing among emerging adults (Seaman & Ikegwuonu, 2011). Thus, these individuals may choose to associate with peers who provide alcohol and/or encourage them to drink heavily. By engaging in a pattern of heavy drinking due to the encouragement of peers, individuals with a sensitivity to subjective feelings of intoxication may ultimately increase their likelihood of blacking out. In line with this, Miller and colleagues (1994) found that self-reported feelings of intoxication during a heavy drinking episode predicted reporting memory impairments the following day. As such, if subjective intoxication serves as a risk factor for blackouts, this effect would be driven, in part, by environmental factors that influence those individuals initiating alcohol use at an early age and subsequently developing a pattern of heavy drinking by emerging adulthood that increases the likelihood that they will report frequently feeling intoxicated when they drink.

Altogether, FH+, early onset of drinking, and subjective responses to alcohol all generate risk for blackouts. This may be due, in part, to high-risk environments, such as having early access to alcohol, parents who have lax views on alcohol use for children, social encouragement to drink, and associating with a deviant peer group. Despite this,

individuals who have a FH+, initiate alcohol use at an early age, or are sensitive to subjective responses to alcohol will not necessarily experience blackouts. Thus, a genetic vulnerability is likely crucial to further explain the differential susceptibility to experiencing these significant negative consequences of alcohol consumption.

Genetic Risk for Blackouts

In fact, there is preliminary evidence for this genetic predisposition to experiencing blackouts. Nelson and colleagues (2004) found that the heritability of ever experiencing blackouts in a lifetime was 52.5%, and the heritability of experiencing three or more blackouts in one year was 57.8% among individuals from the Australian Twin Register database. Others have shown preliminary evidence for a genetic basis to blackouts by finding a significant correlation for the frequency of blackouts among siblings, which they did not find among unrelated individuals (Schuckit et al., 2016b). These findings are promising as a genetic basis to blackouts has been suggested due to our documented inability to explain why not all individuals who drink to a high BAC will experience a blackout (Rose & Grant, 2010; Wetherill & Fromme, 2016; White, 2003).

In examining how genetics underlie risk for blackouts, having a FH+ poses as one potent risk factor for experiencing blackouts (Jennison & Johnson, 1994; LaBrie et al., 2011), suggesting that risk for blackouts may, indeed, be inherited. Because early onset drinkers can develop an increased sensitivity to the effects of alcohol (Israel et al., 2015), this may influence to what extent those individuals will experience alcohol-induced blackouts during emerging adulthood. In line with this notion, Wetherill and Fromme (2009) who found that feelings of sedation and stimulation during a heavy drinking occasion predicted experiencing a blackout during that drinking episode concluded that their findings were, in part, due to a genetic vulnerability towards experiencing blackouts

because they controlled for BAC. Additionally, Schuckit and colleagues (2016a) who found that a low level of response to alcohol predicted experiencing blackouts also controlled for maximum BAC. In contrast to this, an increased sensitivity to subjective feelings of intoxication, one common response to heavy alcohol use, may also increase the likelihood that those individuals will experience blackouts, an effect that would be proposed to be driven by environmental factors associated with alcohol use, as well as genetic factors when controlling for current alcohol consumption.

Further, initiating alcohol use at a young age can have detrimental effects in adolescents' developing brain, especially the hippocampus (Silveri, 2012). For instance, binge drinking during adolescence can affect genetic expression in the hippocampus (Centanni et al., 2014), which may then result in deficits in memory processing. Given the crucial role that the hippocampus plays in memory functioning, altering hippocampal functioning at the neurobiological and possibly genetic expression level can put those individuals at increased risk for experiencing blackouts during emerging adulthood. The investigation of behavioral genetic or molecular genetic mechanisms of blackouts, however, is beyond the scope of the current project, but it is noteworthy that genetic factors likely interact with environmental factors to form a complete explanation of blackouts.

Conceptual Models Linking Risk Factors and Blackouts

Studying these three risk factors specifically, is useful because in addition to being independent risk factors for blackouts, they are also conceptually linked to one another (see Figure 3 & Figure 4). Indeed, one hypothesized connection among these risk factors is that they represent a progression in alcohol consumption that increases risk for blackouts across emerging adulthood (see Figure 3). As detailed above, individuals with a FH+ are more likely to initiate alcohol use at a young age (Dick, 2011), and animal models have found

that an early onset of drinking may then influence whether those individuals will develop an increased sensitivity to the intoxicating effects of alcohol later in life (Israel et al., 2015). This increased sensitivity to subjective feelings of intoxication would be in line with a high level of response to alcohol. Because a high level of response to alcohol is thought to be protective against developing alcohol use disorder, a heritable disorder, (Schuckit, 1994; Schuckit & Smith, 1996), subjective intoxication conferring risk for blackouts would likely be driven, in part, by an underlying genetic predisposition towards experiencing blackouts.

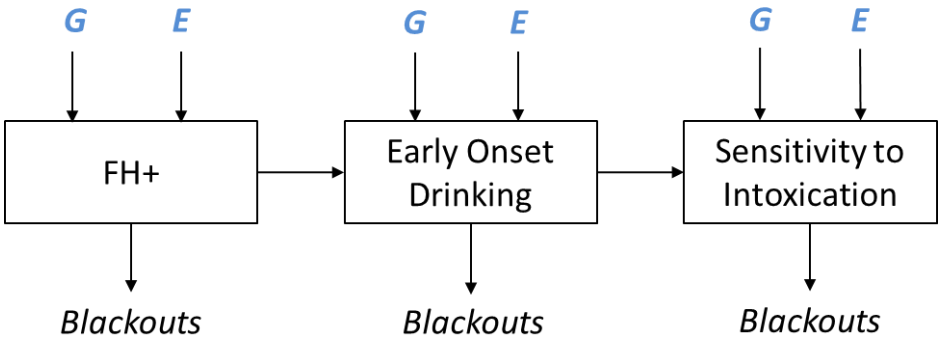

Figure 3. Hypothesis I: Connection among risk factors for blackouts across emerging adulthood

Note: G = Genetics, E = Environment

Indeed, because blackouts are approximately 50% heritable (Nelson et al., 2004), there is an underlying genetic susceptibility towards experiencing these consequences. Given this, a second hypothesis is that FH+, early onset of drinking, and subjective intoxication are connected by a common genetic vulnerability (see Figure 4). Some have found that parents' drinking and drinking to intoxication significantly predicted their children's alcohol consumption at an early age and progression to drinking to the point of

intoxication (Latendresse et al., 2008). Analyzing trajectories of experiencing alcohol-related problems from adolescence through emerging adulthood, others have found that an early onset of drinking, reporting feeling subjectively intoxicated during the first time drinking, and having a FH+ were significant predictors of being classified in a problem-drinking group (Warner, White, & Johnson, 2007). Together, this suggests that FH+, early onset of drinking, and subjective intoxication are conceptually linked to one another by an inherited susceptibility towards consuming alcohol and then experiencing alcohol-related problems. In fact, some have found that an early onset of drinking was associated with the frequency of feeling intoxicated, as well as the frequency of experiencing alcohol-related problems among FH+ individuals but not among FH- individuals (Pilatti, Caneto, Garimaldi, Vera, & Pautassi, 2014). Thus, beyond environmental factors associated with alcohol consumption, these three risk factors may also be connected by a shared inherited genetic vulnerability that explains, in part, how they generate risk for blackouts.

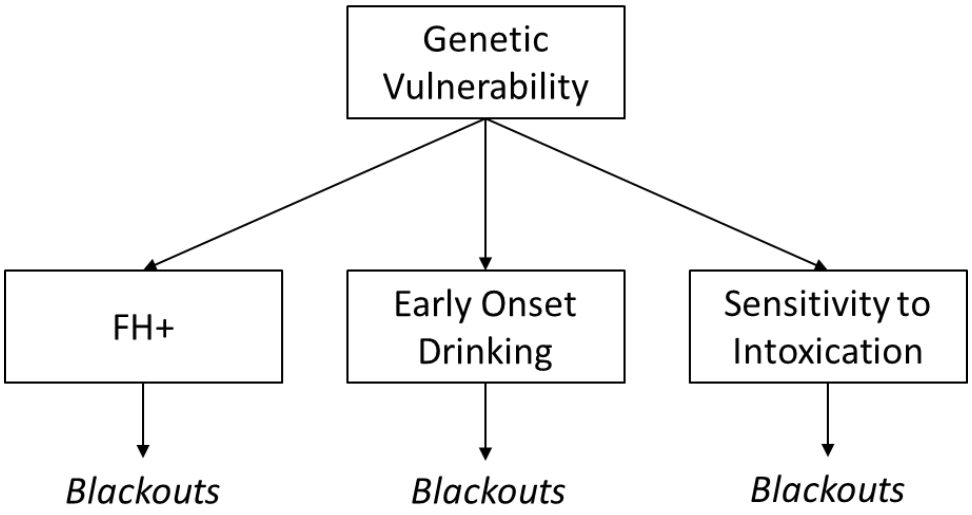

Figure 4. Hypothesis II: Connection among FH+, early onset of drinking, and subjective intoxication conferring risk for blackouts

These two hypothesized models describe inherent connections among FH+, early onset of drinking, and subjective intoxication. Because evidence suggests that these three factors are affected by both the environment and genetics, these proposed models may, in fact, be working concurrently. A progression in alcohol consumption that influences risk for blackouts across emerging adulthood coupled with an inherited genetic vulnerability can help explain the observed differential susceptibility towards experiencing blackouts.

OVERVIEW OF THESE STUDIES

In fact, little is known about how these three individual risk factors (i.e., FH+, early onset of drinking, and subjective intoxication) generate that vulnerability for experiencing blackouts among emerging adults and what this experience might mean for alcohol abuse treatment and making successful behavioral changes. Such gaps in the literature motivated me to produce several testable questions. These questions included the following:

- Does maternal FH+ or paternal FH+ confer greater risk for blackouts, and although women are more likely to experience blackouts, does a maternal FH+ or paternal FH+ differentially affect men and women?
- How do risk factors, such as early onset drinking, affect changes in the frequency of experiencing blackouts over time during emerging adulthood?
- To what extent does subjective intoxication predict experiencing blackouts during the transition out of college?
- Does blacking out produce motivation to decrease drinking, and does this motivation predict successful behavior change in the future?

The first study describes differences in the associations between blackouts and maternal FH+ versus paternal FH+ and how sex of the individual moderates these

associations. This study sheds light on a risk factor that appears to be operating through both genetic and environmental pathways. Specifically, this study is the first to examine the differential effects of maternal FH+ and paternal FH+ and to examine whether men or women may be more at risk for experiencing blackouts with a particular FH+.

The second study is an examination of how early onset drinking affects changes in the frequency of experiencing blackouts across three years using a unique latent factor to measure early onset drinking as a function of ages at first drink, first high, and first drunk. This study describes how the interplay among genetics, neurobiology, and a risky environment can contribute to why early onset drinking is a risk factor for blackouts. In doing so, this is the first study to model growth, or changes, in blackouts over time, and the first to test how early onset drinking affects this growth.

Finally, the third study describes the associations among blackouts, subjective intoxication (i.e., feeling drunk), and motivation to change (e.g., desire to decrease drinking). This study examines the extent to which subjective intoxication serves as a risk factor for experiencing blackouts across the transition out of college. Additionally, this study examines to what extent blackouts predict a motivation to decrease drinking and whether this motivation promotes future changes in drinking behavior. As such, this is the first study to investigate the bidirectional relationship between blackouts and subjective intoxication and how blackouts influence motivation to decrease drinking.

All three studies were conducted using a sample of emerging adults taken from one cohort of incoming college students, and all analyses represent the period of emerging adulthood during the transition out of college and into adult roles. This is a pivotal period for emerging adults as they are tasked with gaining employment and settling into their chosen roles. Thus, emerging adulthood is a period in which they have the freedom to define what their life will be (Arnett, 2000), including to what extent they will consume

alcohol. Given this, emerging adulthood is an important transitional period to examine what factors increase susceptibility towards experiencing negative consequences of alcohol use, especially alcohol-induced blackouts. Overall, the following three studies examine how FH+, early onset of drinking, and subjective intoxication confer risk for blackouts.

Chapter 2: Family History of Problematic Alcohol Use [1]

INTRODUCTION

Although not studied extensively for blackouts, FH+ is also a risk factor for other alcohol-related consequences. For instance, FH+ individuals were more likely to develop alcohol dependence (Sørensen et al., 2011), which speaks to a genetic predisposition for consequences in FH+ individuals. Indeed, FH+ men and women drank more and experienced more negative consequences from their alcohol use compared with FH- individuals of the same sex (LaBrie et al., 2010).

When comparing across sexes, FH+ differentially affects men and women. For example, FH+ was related to negative consequences resulting from alcohol use only for men (Larimer, Anderson, Baer, & Marlatt, 2000). As such, FH+ may be a more powerful risk factor for negative consequences, including blackouts, in men compared with women. This would suggest that men may be more vulnerable than women to the same amount of genetic risk.

To date, few studies have distinguished between maternal and paternal FH+; although, this distinction may be informative for understanding differential risk for negative consequences of heavy drinking. For instance, maternal FH+ in men predicted increased lifetime alcohol use, heavy drinking, drinking problems, and drinking to cope compared with women with a maternal FH+ (Cooper, Peirce, & Tidwell, 1995). Because the majority of the primary caretakers for children continues to be women (Shackelford, Weekes-Shackelford, & Schmitt, 2005), it may be that an alcoholic mother creates more

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[1] Marino, E. N., & Fromme, K. (2015). Alcohol-induced blackouts and maternal family history of problematic alcohol use. *Addictive Behaviors, 45*, 201–206.
Elise N. Marino made the primary contribution to the conceptualization, data analysis, and writing of this study.

distress within the household than an alcoholic father. This distress may then contribute to her male children exhibiting externalizing behaviors, such as problems with substance abuse, whereas her female children may respond with greater internalizing behaviors, such as anxiety and depression (Cooper et al., 1995). One study, however, failed to find a significant association between maternal and paternal FH+ and problematic alcohol use (Chermack, Wryobeck, Walton, & Blow, 2006). Given the contradictory findings regarding maternal and paternal FH+, further research is needed, especially for understudied consequences of heavy drinking, such as blackouts.

Current Study

To address the previously mentioned gap in the literature, the current study was designed to investigate whether maternal or paternal FH+ was more predictive of experiencing blackouts and to what extent sex affected these relationships. Consistent with previous studies (Jennison & Johnson, 1994; LaBrie et al., 2011), we hypothesized that having a FH+ would predict greater likelihood of experiencing blackouts. To expand this research, however, we also separately analyzed the effects of maternal and paternal FH+ on the occurrence of blackouts. Further, we hypothesized that sex would moderate the association between FH+ and blackouts, such that men who have a maternal FH+ would show a greater likelihood of experiencing blackouts than women or those with a paternal FH+. To our knowledge, no study has examined the differential effects of maternal or paternal FH+ on blackouts.

METHOD

Participants

All participants were first-time college freshmen who were recruited the summer before they matriculated into a large, state university in the Southwestern United States.

These data are a result of their participation in a 6-year, longitudinal study examining alcohol use and behavioral risks during the transition from high school through college. Initially, incoming freshman were invited to participate *(N = 6,391)*, and a subset agreed to participate and met the additional inclusion criterion of being unmarried *(n = 4,832)*. Of these, *3,046* participants were randomized to be assessed longitudinally, whereas others were assigned to conditions not relevant to the current analyses. Among those assigned to be assessed longitudinally, those who provided informed consent and completed the baseline survey comprised the longitudinal sample *(n = 2,245)*.

Participants completed online assessments 10 times over the 6 years: high school (baseline), twice a year during Years 1-3, and then once a year during Years 4-6. All participants included in these analyses must have completed assessments for at least baseline and Year 6 (N = 1,164; 65.4% Female), but some may have also completed assessments at Years 4 and 5. Average age at Year 6 was 23.8 years (*SD* = 0.4), 701 (60.2%) participants were Caucasian, 259 (22.3%) were Asian, 46 (4.0%) were Black, and 158 (13.5%) reported other races.

Measures

Demographics

Participants reported demographic information, including sex and race, which were used in all of our analyses.

Alcohol-Induced Blackouts

A single item asked respondents to report the frequency with which they "had difficulty remembering things you said or did or events that happened while you were drinking" during the past 3 months. Responses were coded on a 5-point Likert-type scale, where 1 = never, 2 = some of the time, 3 = half of the time, 4 = most of the time, and 5 =

always. Blackouts were dichotomized (yes/no) with a response of 2 or greater at Years 4-6 being coded as positive. We used Years 4-6 because we did not add our expanded definition of blackouts until the Year 4 survey. We aggregated blackouts across these three years in order to more broadly capture the prevalence of blackouts because assessments only asked about the previous three months.

Family History of Problematic Alcohol Use

FH+ was assessed at baseline using the Family Tree Questionnaire (Mann, Sobell, Sobell, & Pavan, 1985), a self-report measure that asks about the alcohol use of mother, father, grandparents, and siblings. Response options were: never drank, social drinker, possible problem drinker, and definite problem drinker. Respondents were coded as FH+ if they reported a mother, father, or any of their four biological grandparents as a possible or definite problem drinker (Vaughan, Corbin, & Fromme, 2009). Overall FH+ was calculated using mother, father, and all four grandparents. Maternal FH+ was calculated using mother, maternal grandmother, and maternal grandfather. Paternal FH+ was calculated using father, paternal grandmother, and paternal grandfather. FH+ was calculated if one or more members of the family were probable or definite problem drinkers.

Alcohol Use

The Daily Drinking Questionnaire (DDQ; Collins, Parks, & Marlatt, 1985) measured participants' alcohol use in terms of quantity and frequency of typical drinking during the past 3 months. Using an open-ended response format, participants indicated the number of standard drinks they consumed on each day in a typical week during the past 3 months. Frequency was calculated as the average number of drinking days, and quantity was calculated as the average number of drinks per drinking day. Number of drinks was

calculated based on standard drinks, where a standard drink was defined as 1.5 fluid ounces of liquor, 12 fluid ounces of beer, or five fluid ounces of wine.

Procedure

All procedures were approved by the university's Institutional Review Board, and all participants provided informed consent. Initially, all members of the entering class of 2004 were approached in person during orientation or by postal mail during the summer before classes began. If they were never married and completed the baseline survey, they were eligible for randomization into the study. Participants were emailed a link to the surveys at ten time points: summer before college; fall and spring semesters of freshman, sophomore, and junior years; and fall semester of senior year and the following two years. Further detail regarding recruitment and email methodology are published elsewhere (Hatzenbuehler, Corbin, & Fromme, 2008). Participants were compensated $30 for baseline, $20 for fall surveys during Years 1-3, $25 for spring surveys during Years 1-3, and $40 each for Years 4-6.

Statistical Analysis

Analyses were performed using SPSS Version 18. First, in order to characterize those who experienced blackouts, we examined the bivariate relations among demographics by blackout status. Bivariate comparisons were computed using χ^2 tests for categorical variables and two-tailed *t*-tests for continuous variables. Next, we calculated the sex distribution of those reporting an overall, maternal, and paternal FH+ using χ^2 tests to ensure that there were no significant sex differences in rates of FH+ that might bias our moderation analyses.

Using three logistic regression models, we examined whether overall, maternal, and paternal FH+ predicted likelihood of experiencing blackouts. For our moderation analyses,

we then examined whether there was a significant interaction between sex and overall, maternal, or paternal FH+. The dichotomous outcome measure was any self-reported blackouts across Years 4-6. Because blackouts occur most often after excessive drinking (Jennison & Johnson, 1994) and at higher BACs (White, 2003), we controlled for past 3 month quantity and frequency of drinking. Additionally, due to evidence of differential pathways to alcohol dependence by race (Akins, Smith, & Mosher, 2010; Alvanzo et al., 2011), we controlled for race.

RESULTS

Overall, 773 (66.4%) participants reported blackouts, and 441 (37.9%) reported an overall FH+. Additionally, 240 (20.6%) reported a maternal FH+, and 315 (27.1%) reported a paternal FH+. The average number of drinking days in a typical week was 1.4 (*SD* = 1.4), and the average number of drinks per drinking day was 2.5 (*SD* = 2.7).

Participant Characteristics (N = 1,164)	Blackouts Yes (n = 773)	Blackouts No (n = 391)	*p* value
Demographics			
Female	499 (64.6%)	262 (67.0%)	.406
Caucasian	489 (63.3%)	212 (54.2%)	.003
Age	23.8 (0.4)	23.7 (0.4)	.118
Alcohol Use (past 3 months)			
Quantity of alcohol use (drinks/drinking day)	3.1 (3.1)	1.4 (1.4)	< .001
Frequency of alcohol use (drinking days/week)	1.7 (1.5)	0.8 (1.1)	< .001
Family History of Problematic Alcohol Use (FH+)			
Overall FH+	311 (40.2%)	130 (33.2%)	.020
Maternal FH+	170 (22.0%)	70 (17.9%)	.103
Paternal FH+	227 (29.4%)	88 (22.5%)	.013

Table 1. Bivariate analyses of demographic and clinical characteristics by blackout status

Notes: Mean (SD) or n (%).

First, we analyzed differences among those who did and did not report blackouts. As shown in Table 1, bivariate comparisons indicated that those who reported blackouts were significantly more likely to be Caucasian ($p = .003$), drink more frequently ($p < .001$), drink in greater quantities ($p < .001$), have an overall FH+ ($p = .02$), and have a paternal FH+ ($p = .02$). The association between maternal FH+ and blackouts was not significant in a bivariate comparison.

We then examined whether there were sex differences in our three FH+ variables and found no significant differences by sex for any of the FH+ variables, all ps > .05 (Table 2). Thus, we concluded that there would be no significant sex bias for our moderation analyses in the subsequent multivariate models.

Participant Characteristics (N = 1,164)	Female (n = 761)	Male (n = 403)	*p* value
Family history of problematic alcohol use (FH+)			
Overall FH+	302 (39.7%)	139 (34.5%)	.082
Maternal FH+	164 (21.6%)	76 (18.9%)	.280
Paternal FH+	217 (28.5%)	98 (24.3%)	.126

Table 2. Bivariate analyses of FH+ by sex

Notes: n (%).

Next, we performed three separate logistic regressions for each FH+ predictor (Table 3). In all three models, greater quantity (adjusted odds ratio (aOR) = 1.64, 95% confidence interval (CI) [1.47, 1.83]) and greater frequency (aOR = 1.36, 95% CI [1.18, 1.56]) of drinking were significantly associated with blackouts. Further, a significant main effect for sex (aOR = 1.42, 95% CI [1.03, 1.96]) indicated that compared with men, women were significantly more likely to report blackouts. We then examined whether FH+

predicted the likelihood of blackouts, and results indicated that no FH+ variable significantly predicted blackouts. Having a maternal FH+, however, trended toward a greater likelihood of reporting blackouts (p = .064).

Despite a lack of main effects of FH+ on the likelihood of blackouts, we proceeded with our a priori hypothesis that the effect of FH+ would be moderated by sex. After controlling for race and quantity and frequency of drinking, the interaction among maternal FH+ and sex was significant (aOR = 0.45, 95% CI [0.20, 0.99]), indicating that men but not women with a maternal FH+ were significantly more likely to report blackouts. Conversely, neither overall FH+ by sex nor paternal FH+ by sex significantly predicted likelihood of blackouts.

Overall FH+	
Race	0.92 [0.69, 1.23]
Quantity of drinking	1.64 [1.47, 1.83] ǂ
Frequency of drinking	1.35 [1.18, 1.55] ǂ
Sex	1.37 [0.96, 1.95]
Overall FH+	1.49 [0.89, 2.51]
Sex x Overall FH+	0.73 [0.39, 1.36]
Paternal FH+	
Race	0.93 [0.70, 1.24]
Quantity of drinking	1.65 [1.48, 1.84] ǂ
Frequency of drinking	1.34 [1.17, 1.54] ǂ
Sex	1.17 [0.84, 1.63]
Paternal FH+	1.11 [0.63, 1.97]
Sex x Paternal FH+	1.23 [0.62, 2.45]
Maternal FH+	
Race	0.92 [0.69, 1.22]
Quantity of drinking	1.64 [1.47, 1.83] ǂ
Frequency of drinking	1.36 [1.18, 1.56] ǂ
Sex	1.42 [1.03, 1.96] *
Maternal FH+	1.92 [0.96, 3.81]
Sex x Maternal FH+	0.45 [0.20, 0.99] *

Table 3. Logistic regression coefficients for overall, paternal, and maternal FH+ on blackouts

Notes: * $p < .05$, ǂ $p < .001$; adjusted odds ratios [95% confidence intervals].

DISCUSSION

Based on evidence that genetic factors contribute to alcohol dependence (Kendler, Aggen, Prescott, Crabbe, & Neale, 2012) and blackouts (Nelson et al., 2004), we examined the association among these two alcohol-related consequences. Among our sample of first-time university students, 37% had an overall FH+, and 66% reported blackouts. We further examined the independent effects of maternal and paternal FH+ on the likelihood of

blackouts. Consistent with previous research (Jennison & Johnson, 1994; LaBrie et al., 2011; White et al., 2004; White, 2003), analyses indicated that those who reported blackouts were more likely to be female, Caucasian, frequent, heavy drinkers who reported an overall FH+, and a paternal FH+. Once we controlled for race and typical drinking in the multivariate models, however, neither overall nor paternal FH+ had a main effect on the experience of blackouts. Despite this, our hypothesis-driven moderation analyses revealed that sex interacted with FH+, such that men with a maternal FH+ were more than twice as likely to report blackouts compared with women with a maternal FH+. Genetic and environmental factors may help explain this finding.

Consistent with our findings, early studies suggested that the genetic heritability of alcohol use disorders was greater in men than women (McGue, Pickens, & Svikis, 1992). Recent research, however, indicates that the genetic heritability of alcohol dependence and drinking is equal across sexes (Beek, Moor, Geels, Willemsen, & Boomsma, 2014; Heath et al., 1997; Hicks, Krueger, Iacono, McGue, & Patrick, 2004). In other words, there appears to be equal genetic susceptibility towards alcohol dependence and alcohol consumption in men and women, which is in line with a diminishing sex gap in prevalence rates of alcohol use and related consequences (Keyes, Li, & Hasin, 2011). Whereas this indicates that there is equal genetic heritability of alcohol-related problems among men and women, our findings suggest that men may be more vulnerable than women to the same amount of genetic risk.

Specifically, our results indicate that the genetic risk for blackouts is transferred from mother to son. This pattern of stronger genetic transmission by mothers is also evident in several psychological disorders. For instance, in Alzheimer's disease (Mosconi et al., 2010) and bipolar disorder (McMahon, Stine, Meyers, Simpson, & DePaulo, 1995), children with an affected mother are at greater risk of developing the disorder compared

with children with an affected father. In addition, consistent with our findings, the sons of mothers with schizophrenia were twice as likely to develop psychosis compared with daughters (Goldstein et al., 2011). All three disorders have a strong genetic component (Gatz et al., 2006; Lichtenstein et al., 2009; Wray & Gottesman, 2012), and evidence indicates that an affected mother, as opposed to an affected father, confers greater risk for development of the disorder in the child. Moreover, with evidence that women need higher genetic risk to reach a threshold for neurodevelopmental disorders than men (Jacquemont et al., 2014), we might expect stronger genetic transmission from mothers to sons. Our results are consistent with the idea that a maternal FH+ produces sufficient genetic risk to push men, but not women, over the threshold for experiencing the neurocognitive phenomena of blackouts.

In conjunction with a genetic predisposition, a maternal FH+ may produce a high-risk environment for the initiation of problematic drinking. For instance, if the mother is dependent on alcohol, and especially if she is the primary caretaker, the children have ample opportunities to witness her modeling of maladaptive drinking. Additionally, there may be lower parental monitoring, contributing to a chaotic environment that creates stress in the children. As a consequence, men may be more likely to abuse alcohol as a method of coping with the stress of having an alcoholic mother, a theory that has been previously proposed (Cooper et al., 1995). That is, their genetic vulnerability towards heavy drinking, as a result of having a maternal FH+, may lead men to use alcohol as a means of coping with a stressful family environment.

Further, a mother who is dependent on alcohol and/or who grew up with alcoholic parents may have more permissive views about alcohol use, especially for her son. These views can promote an environment whereby drinking may be perceived as acceptable and alcohol may be readily available. This type of environment is problematic as early initiation

of alcohol use is largely determined by social/environmental factors, such as family and peers (Dick, 2011). Moreover, early onset of drinking is one predictor of blackouts (Jennison & Johnson, 1994; White et al., 2002). As such, environments that provide access to alcohol and condone drinking, especially for boys, can lead to early alcohol use, which may start a pattern of heavy drinking that can carry forward into adulthood. An established pattern of heavy drinking then leads to blackouts, especially in genetically vulnerable men.

Given this, it is likely that the genetic predisposition passed from the mother is working in parallel with the risky environment she may create to produce a greater likelihood that her son will experience blackouts. Because a maternal FH+, specifically for men, is associated with heavy alcohol use, alcohol-related negative consequences (Cooper et al., 1995), and now blackouts, genetic vulnerability coupled with a risky environment likely drives this association. Indeed, research indicates that genetics have a greater influence on alcohol use when there is an environment with low parental monitoring or high alcohol availability (Kendler, Gardner, & Dick, 2011). Ultimately, because evidence clearly demonstrates that heavy drinking leads to blackouts, those genetically vulnerable men who grew up in an environment that allowed or encouraged alcohol use have an increased likelihood of later experiencing blackouts.

Given these findings, targeted prevention programs might focus on men with a maternal FH+ as they are at high risk for blackouts. Because men with a maternal FH+ could possibly be identified at a young age, these interventions might begin with children as early as elementary school age. Consequently our findings may inform prevention programs that educate families about alcohol and its negative consequences, such as the Strengthening Families Program (Spoth, Reyes, Redmond, & Shin, 1999) and Raising Healthy Children Project (Brown, Catalano, Fleming, Haggerty, & Abbott, 2005).

Limitations

Some caveats of our study should be mentioned. Assessments were self-report and retrospective as participants were asked to report on their blackouts and perception of family's drinking patterns. In addition, the majority of the study sample was Caucasian; although, it reflected the heterogeneity similar to other academic institutions in the geographical area. Participants also began the study as university freshmen, so findings may not generalize to other populations. Further, while it is challenging to study blackouts, alcohol self-reports are reliable and valid (Del Boca & Darkes, 2003), and blackouts are an accepted phenomena (e.g., Rose & Grant, 2010).

Conclusions

Despite limitations, findings come from a prospective study that spanned 6 years with a relatively large and ethnically diverse sample, which provided an opportunity to examine drinking patterns and blackouts during the transition into adulthood. Our findings extend the extant literature by demonstrating that a maternal FH+ is a risk factor for blackouts in men. Whereas replication of our findings is needed, they are an important step toward understanding a significant yet understudied consequence of heavy drinking that is especially salient among young adults.

Chapter 3: Early Onset Drinking [2]

INTRODUCTION

Despite the legal drinking age being 21 in the United States, many individuals initiate alcohol use at an earlier age. This is problematic as a young age at first drink leads to myriad consequences. For instance, those who consumed their first drink before age 15 were more likely to experience negative neurological, physical, and psychological consequences, including alcohol-induced blackouts (Jennison & Johnson, 1994), hangovers, and needing greater amounts of alcohol to achieve the same intoxicated feeling (LaBrie, Rodrigues, Schiffman, & Tawalbeh, 2008) compared with those who consumed their first drink after age 15. A young age at first drink is also associated with the development of alcohol dependence (Dawson et al., 2008; Hingson, Heeren, & Wechsler, 2003; Hingson, Heeren, & Winter, 2006).

Whereas early onset drinking is often conceptualized as first drink, an early age of first becoming intoxicated may also be an important developmental marker. Whereas first drink could mean taking a sip of alcohol, first intoxication corresponds to the first drinking episode in which an individual consumed enough alcohol to feel subjectively intoxicated. Similar to a young age at first drink, those with a first subjective intoxication before age 14 were more likely to develop alcohol dependence compared with those who had a first subjective intoxication at or after age 21 (Hingson et al., 2006). As such, a young age at first drink and a young age at first intoxication appear to predispose one to similar alcohol-related consequences.

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[2] Marino, E. N., & Fromme, K. (2016). Early onset drinking predicts greater level but not growth of alcohol-induced blackouts beyond the effect of binge drinking during emerging adulthood. *Alcoholism: Clinical and Experimental Research, 40*(3), 599-605.
Elise N. Marino made the primary contribution to the conceptualization, data analysis, and writing of this study.

Binge drinking, often characterized as consuming four or more drinks for women and five or more drinks for men on one occasion, is also associated with many of the same consequences as early onset drinking, including alcohol use disorders and alcohol-induced blackouts (White & Hingson, 2014). In addition, blackouts are most likely to occur during binge drinking episodes because blackouts typically result from consuming large amounts of alcohol, often in a short period of time (Jennison and Johnson, 1994; White, 2003; White et al., 2004).

Addressing Gaps in the Literature

Despite evidence that an early age at drinking onset and binge drinking are both associated with experiencing blackouts (Jennison and Johnson, 1994; White and Hingson, 2014), possible changes in the occurrence of blackouts across time for early onset drinkers has yet to be examined. It is not known, for example, whether early exposure to alcohol might sensitize the brain and predispose one to experiencing alcohol-induced blackouts after accounting for levels of binge drinking over time. Further, it is not known whether changes in binge drinking translate to changes in the frequency of blacking out and how early onset drinking may affect these changes.

Consequently, the objective of this study was to examine how early onset drinking may influence both the level and changes in the experience of alcohol-induced blackouts across time. By controlling for year-specific binge drinking, we separated the influence of early onset drinking on blackouts from the environmental predisposing factor of heavy drinking. Thus, we examined a full model that accounts for early onset drinking, binge drinking, and alcohol-induced blackouts in order to provide explanatory clarity in a multivariate framework in a non-clinical, diverse sample.

MATERIALS AND METHODS

Participants and Procedure

Participants were part of an incoming class of first-time college freshmen who were recruited during the summer before they enrolled at a large state university in the Southwestern United States. These data come from the 6-year, longitudinal arm of the study which examined alcohol use and behavioral risks during the transition from high school through college. Initially, 6,391 students were invited to participate, and 4,832 indicated an interest in the study and met the inclusion criterion of being unmarried. Among these, 3,046 participants were randomized to be assessed longitudinally, and the remainder was assigned to assessment conditions not pertinent to the current study. The final longitudinal sample included 2,245 who provided informed consent and completed the baseline survey (see Corbin et al., 2008 for further description of these samples).

There were ten assessments over six years: baseline (high school), biannually during Years 1-3, and annually during Years 4-6. Participants included in these analyses (N = 1,145) must have completed the Year 4 survey and reported consuming their first drink by this wave of data collection. Overall, 67.9% were female, and 62.2% were Caucasian, 20.1% were Asian, 3.9% were Black, and 13.8% reported other ethnicities. Average age at Year 4 was 21.8 years (*SD* = 0.3).

The study received Institutional Review Board approval, and all participants provided informed consent. They were contacted by email to complete web-based surveys. Participants were compensated $40 for each survey during Years 4-6.

Measures

Early Onset Drinking

Early onset drinking was a latent factor that was regressed onto age at first drink, first high, and first drunk in order to capture both objective and subjective indices of early onset drinking. In the measurement model, which demonstrated perfect fit, all three indicators were statistically significant: first drink (b = 1.444, $p < .001$), first high (b = 1.819, $p < .001$), and first drunk (b = 1.638, $p < .001$). Participants were asked to report how old they were when they "took your first drink on your own" (first *drink*), further specifying that this excluded drinking from a parent's glass or drinking as part of a religious ceremony. In addition, participants were asked to report how old they were when they "first got high or lightheaded after drinking alcohol" (first *high*), and "first got drunk after drinking alcohol" (first *drunk*). Response options on a 9-point Likert-type scale were: never, $\leq$ 9, 10-12, 13-15, 16, 17, 18, 19, and $\geq$ 20. Ages were coded as 9, 11, 14, 16, 17, 18, 19, and 20. While all participants included in these analyses reported consuming their first drink, some reported never feeling high or drunk. Those individuals were coded at the oldest age. For the growth curve analysis, ages were reverse coded in order to test whether younger ages at drinking onset were positively associated with experiencing blackouts. We used age at first drink, first high, and first drunk reported at Year 4, which was the first time participants provided this data, to create our latent factor of drinking onset.

Binge Drinking

Using items adapted from Wechsler and Isaac (1992), participants provided an open-ended response to the question: "during the past three months, how many times did you have four/five [women/men] or more drinks in one sitting?"

Alcohol-Induced Blackouts

One question asked participants to indicate the frequency with which they "had difficulty remembering things you said or did or events that happened while you were drinking" during the past three months. The response format was a 5-point Likert-type scale, where 1 = never, 2 = some of the time, 3 = half of the time, 4 = most of the time, and 5 = always. In order to describe differences between those who did and did not report experiencing blackouts, we dichotomized this measure across all three years as yes/no for experiencing any blackouts. For our main analysis (growth curve model), we used the Likert coding as a measure of frequency of experiencing blackouts.

Demographics

Sex and race were assessed at the baseline survey. They were used in the bivariate analyses by attrition and blackouts status. Sex was also entered as a covariate in the growth curve analysis.

Baseline Alcohol Use

In order to compare the sample used in the current study with those from the final longitudinal sample who were excluded from these analyses, we assessed two facets of alcohol use at baseline. Binge drinking was measured in the same manner as previously described. Alcohol-induced blackouts at baseline was taken from the Rutgers Alcohol Problem Index (White & Labouvie, 1989). This item asked respondents if they "suddenly found yourself in a place that you could not remember getting to." It was dichotomized as yes/no for experiencing blackouts. Whereas this is a narrow definition of blackouts, we did not add our expanded definition of blackouts until the Year 4 survey.

Statistical Analysis

We used SPSS Version 18 to examine the bivariate associations of demographic and baseline alcohol use characteristics between those who were included versus excluded from our analyses in order to determine if our sample was representative of the overall sample from which our data are drawn. In addition, we performed bivariate analyses between those who did and did not report experiencing any alcohol-induced blackouts by comparing these groups on demographic and alcohol use characteristics. Chi-square tests were used to examine categorical variables, and two-tailed *t*-tests were used to examine continuous variables.

Next, using Mplus Version 7 (Muthén & Muthén, 1998), we used growth curve modeling (McArdle & Nesselroade, 2003) to estimate the effect of early onset drinking on the growth parameters of experiencing alcohol-induced blackouts across three years. This particular type of structural equation modeling estimates three latent, unobserved factors: intercept *(I),* linear slope *(S),* and quadratic slope *(Q)* in order to measure change over repeated assessments (i.e., time). These three latent factors estimate the mean level of the outcome variable at the initial time point or where the sample starts *(I),* the linear growth across all assessments *(S),* and any non-linear (i.e., quadratic) growth across all assessments *(Q).* In contrast to the linear slope, the quadratic slope can account for acceleration or deceleration across time.

RESULTS

Attrition Analyses

In total, 3,046 individuals were randomized to be assessed longitudinally. Of these, 2,245 participants completed the baseline survey and comprised the final longitudinal sample. Those who completed the first survey were more likely to be female and lighter

drinkers with no racial/ethnic difference compared with those who did not complete the first survey (see Corbin et al., 2008).

The current study includes 1,145 (51.0%) of the original longitudinal sample of 2,245. Inclusion in these analyses required participants to have completed the Year 4 survey and consumed their first drink by this wave of data collection. As shown in Table 4, those included in the current analyses were more likely to be women ($p < .001$) and Caucasian ($p = .006$) compared with those who were excluded. The two groups did not differ in age ($p = .068$), number of binge drinking episodes in the past 3 months at baseline ($p = .819$), or alcohol-induced blackouts at baseline ($p = .471$). Given this, we concluded that the sample for our analyses was representative of the overall sample in terms of alcohol use and related consequences.

Participant Characteristics (N = 2,245)	Included [a] (n = 1,145)	Excluded [a] (n = 1,100)	*p* value
Demographics			
Female	776 (67.8%)	569 (51.6%)	< .001
Age	18.4 (0.3)	18.4 (0.4)	.068
Caucasian	712 (62.2%)	622 (56.4%)	.006
Alcohol Use			
Number of binge drinking episodes in past 3 months	2.1 (5.8)	2.2 (5.0)	.819
Alcohol-induced blackouts [b]	89 (7.8%)	95 (8.7%)	.471

Table 4. Attrition analyses: Bivariate comparisons of participants' baseline characteristics by inclusion in the current study

Notes: n (%) or mean (SD). Comparisons all made at the baseline survey. [a] 2,245 who completed the baseline survey comprised the full longitudinal sample. Bivariate comparisons were made between those from that sample who were included versus excluded from the current study. [b] Based on the Rutgers Alcohol Problem Index blackouts item.

Participant Characteristics

All participants had consumed their first drink by Year 4 (N = 1,145), but 8.2% reported that they had never felt high after drinking, and 12.2% reported that they had never felt drunk. Overall, 69.2% reported blackouts during Years 4-6. Finally, the average number of binge drinking episodes decreased over the three-year period (Year 4: $M = 5.00$ ($SD = 7.9$), Year 5: $M = 3.9$ ($SD = 6.8$), Year 6: $M = 3.3$ ($SD = 6.4$)).

As shown in Table 5, there were significant bivariate differences among those who did and did not report experiencing any blackouts across the three years. For these descriptive purposes only, alcohol-induced blackouts were dichotomized as yes/no for experiencing any blackouts during Years 4-6. Those who reported blackouts were more likely to be Caucasian ($p = .005$), had their first drink at a younger age ($p < .001$), reported feeling subjectively intoxicated (i.e., high and drunk) for the first time at a younger age ($p < .001$), and reported binge drinking more often ($p < .001$) compared with those who did not report blackouts.

Participant Characteristics (N = 1,145)	Blackouts Yes (n = 792)	Blackouts No (n = 353)	*p* value
Demographics			
Female	534 (67.4%)	243 (68.8%)	.636
Age at Year 4	21.8 (0.3)	21.7 (0.4)	.158
Caucasian	514 (64.9%)	198 (56.1%)	.005
Alcohol use			
Age at first *drink*	16.0 (2.5)	17.3 (2.6)	< .001
Age at first *high* [a]	16.8 (2.1)	18.0 (2.1)	< .001
Age at first *drunk* [a]	17.1 (2.1)	18.1 (1.9)	< .001
Year 4 binge drinking [b]	6.8 (8.7)	1.0 (2.5)	< .001
Year 5 binge drinking [b]	5.5 (7.8)	1.0 (2.6)	< .001
Year 6 binge drinking [b]	4.7 (7.4)	0.8 (2.6)	< .001

Table 5. Bivariate analyses of participants' demographic characteristics and alcohol use by the experience of any blackouts during Years 4-6

Notes: n (%) or mean (SD). [a] Among only those reporting an age at first high or first drunk. [b] Number of binge drinking episodes in the past 3 months at each year.

Growth Curve Model

Using Maximum Likelihood Robust estimation, the growth curve analysis measured the effect of early onset drinking on the growth parameters of a continuous measure of alcohol-induced blackouts across three years, controlling for the effect of sex on blackouts (see Figure 3). Because binge drinking, our time varying covariate, was positively skewed, it was treated as a count variable in the model, and as such, we specified a negative binomial distribution. Consequently, traditional model fit statistics are unavailable, but the Akaike Information Criteria (AIC) and the Bayesian Information Criteria (BIC) (Akaike, 1987; Sclove, 1987) statistics were calculated for our final model (AIC = 34709.511 and BIC = 34860.806).

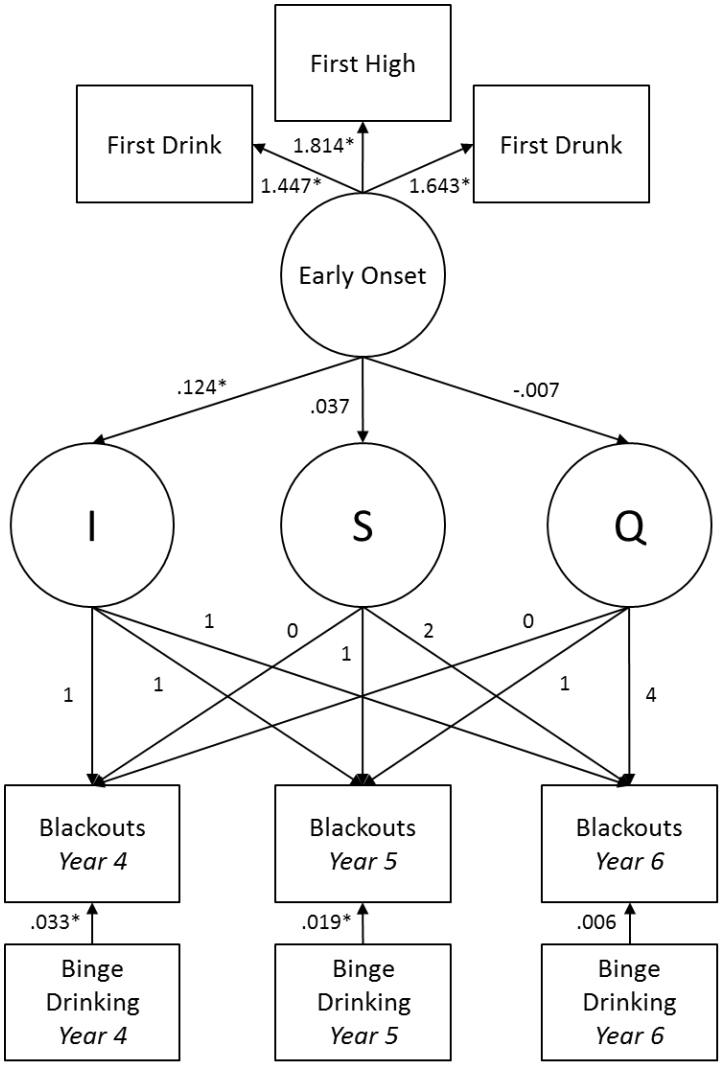

Figure 5. Growth curve model for alcohol-induced blackouts by early onset drinking across three years

Notes: * indicates a statistically significant path at $p < .001$. All paths are unstandardized estimates. Covariate included in the model was sex, which was regressed onto the intercept *(I)*, slope *(S)*, and quadratic slope *(Q)* of alcohol-induced blackouts.

The early onset latent factor was just identified and, thus, demonstrated perfect fit. We conducted a Wald test to determine if the effect of binge drinking could be constrained to be equal across time. A significant result (p = .038) indicated that the effect of binge drinking on blackouts did change over time and, thus, could not be constrained to be equal. Results suggested that the effect of binge drinking on blackouts decreased over time (see Figure 3), which is consistent with the decrease in the number of binge drinking episodes, despite a stable level of blackouts. Further, because women are more likely to experience blackouts, we included sex as a covariate on the growth parameters of blackouts (i.e., *I, S, Q*). The only significant sex effect was on the intercept, indicating that women were more likely to show a higher level of experiencing blackouts at Year 4 (b = -.088, 95% confidence interval (CI) [-.170, -.005], p = .037). We also tested whether there was a significant time varying interaction between binge drinking and sex on blackouts; however, we found no significant binge drinking by sex interactions on blackouts across time.

As shown in Figure 4, early onset drinkers are experiencing more frequent blackouts at Year 4 (b = 0.124, 95% CI [.078, .170], p < .001). When examining the linear slope, there was no significant increase or decrease in blackouts by early onset drinking (b = 0.037, 95% CI [-.057, .131], p = .443). Further, based on the quadratic slope, there was no significant acceleration or deceleration in the frequency of blackouts across time by early onset drinking (b = -0.007, 95% CI [-.055, .041], p = .770). As such, early onset drinkers continued to experience greater levels of blackouts over time, but they did not demonstrate differential growth or change in reported blackouts, despite the fact that the effect of binge drinking on blackouts decreased across the three years.

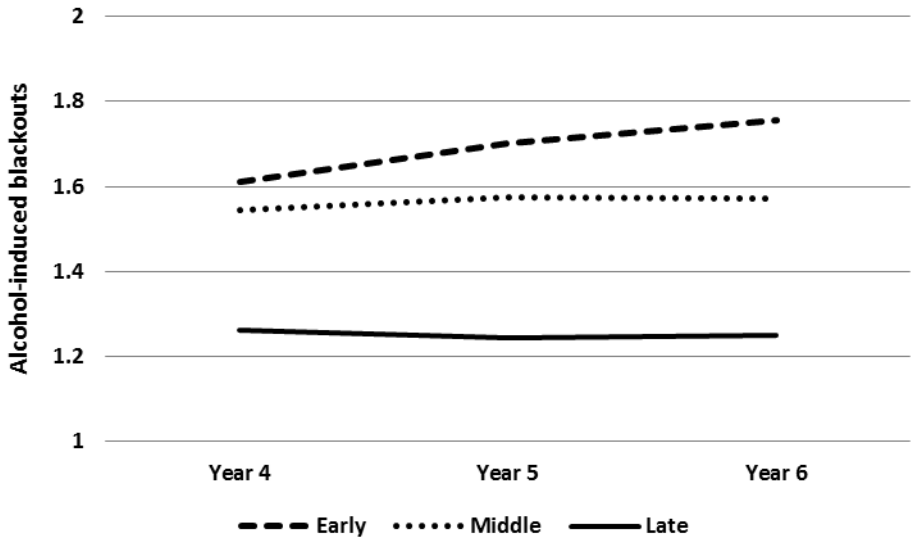

Figure 6. Predicted frequency of alcohol-induced blackouts by early onset drinking

Notes: Covariate included in the model was sex; time varying covariates included in the model were year-specific binge drinking. Frequency of alcohol-induced blackouts is based on a Likert scale (1-5). Early, Middle and Late categories represent -1 standard deviation (SD), the mean, and +1 SD of the latent Early Onset factor, respectively.

DISCUSSION

This study examined the effect of early onset drinking on the growth parameters of alcohol-induced blackouts across three years using a latent factor of age at drinking onset (i.e., age at first drink, first high, and first drunk). Findings indicate that those who started drinking earlier were more likely to show greater levels of blackouts compared with those who initiated alcohol use later. Analyses also indicated that there was no significant acceleration or deceleration in blackouts across time, demonstrating that early onset

drinkers continued to experience frequent blackouts even though the average number of binge drinking episodes decreased. Overall, these findings indicate that there are likely unique neurobiological and possibly genetic factors contributing to the experience of blackouts that are stemming from early alcohol initiation above and beyond those explained by time-varying patterns of binge drinking.

Adolescence is an important period for the final phases of neural maturation (Biagi et al., 2007). During this time, heavy alcohol use can affect the development of brain regions and interfere with cognitive functioning. For instance, individuals who consumed their first drink before age 14 demonstrated neurocognitive deficits and neurodegeneration in brain regions responsible for learning and memory (Zeigler et al., 2005). Further, binge drinking adolescents have impaired visuospatial memory and attention, as well as abnormal brain activation signaling neurocognitive deficits (Squeglia et al., 2009, 2012). As such, initiating alcohol use during adolescence when the brain is more susceptible to the damaging pharmacological effects of alcohol causes the brain to be more vulnerable to the effects of alcohol later in life compared with alcohol exposure during adulthood (Israel et al., 2015). This includes being more susceptible to alcohol-induced hippocampal dysregulation, which leads to memory deficits (Silveri, 2012). For instance, adolescent rats exposed to binge drinking demonstrated poorer working memory than rats exposed to binge drinking during adulthood (White, Ghia, Levin, & Swartzwelder, 2000a), possibly due to hippocampal neurotoxicity or NMDA receptor hyper excitability resulting from heavy alcohol use. Overall, the effect of early alcohol use appears to alter neural functioning, in particular memory.

In turn, the detrimental effect of early onset drinking on neural functioning may be related to the neuroanatomical development that occurs during adolescence, especially in brain regions responsible for memory, which could have lasting negative effects into

adulthood. Indeed, animal models have shown that binge drinking during adolescence alters the synaptic structure of the hippocampus, causing functional abnormalities (Risher et al., 2015), as well as producing alterations in GABA receptor subtype expression in the hippocampus (Centanni et al., 2014). Further, similar detrimental effects have been found in human studies, including hippocampal atrophy in adolescents who binge drink frequently (Welch, Carson, & Lawrie, 2013). Given the integral part the hippocampus plays in memory formation, processing, and retrieval, these enduring developmental and structural changes due to early alcohol use may cause the brain to be more vulnerable to the pharmacological effects of alcohol on memory during emerging adulthood. This may then explain why early alcohol use increases susceptibility to experiencing the neurobiological phenomena of alcohol-induced blackouts and why early onset drinkers continue to experience more frequent blackouts over time despite a decrease in binge drinking, one powerful risk factor for blackouts.

Future Directions

Genetic factors, such as alterations in GABA, NMDA receptors, and brain-derived neurotrophic factors (BDNF) (all known to influence cognition, memory, and potentially blackouts) (Nelson et al., 2004) may help further explain why initiating alcohol use at a young age is associated with the experience of blackouts. We are currently collecting DNA in order to look at the genetic underpinnings of alcohol-induced blackouts. Future studies might also examine whether genetic factors predict differences in developmental trajectories of blackouts. For example, (Schuckit et al., 2015) have identified trajectory classes of experiencing any blackouts (yes/no) from middle to late adolescence, but it is unknown whether genetic factors can predict class membership in such a model. In addition, other potential early environmental factors that are associated with problematic

drinking and alcohol-related consequences, such as childhood adversity or trauma (Carlson, Harden, Kretsch, Corbin, & Fromme, 2015; Smith, Smith, & Grekin, 2014), can be explored as possible gene x environment interactions that increase the likelihood of experiencing blackouts for early onset drinkers.

Limitations

Our study has several limitations, including the survey methodology, which precludes any conclusions about causality. In particular, participants self-reported the age at which they began drinking, felt high/lightheaded for the first time, and felt drunk for the first time at Year 4 of the larger 6-year longitudinal study. Further, participants also self-reported the number of times that they binge drank and whether they experienced blackouts during a three-month period at each annual assessment. As retrospective measures, they may be biased by the passing of time or inaccurate recall, however, the collection of multiple waves of data increase confidence in the reported experiences. Lastly, these data were gathered from a college sample, limiting the generalizability to the broader population.

Conclusions

Despite the aforementioned caveats, these findings come from a longitudinal study over three years with a large, ethnically diverse sample, which strengthens our findings by allowing us to prospectively examine early onset drinking, binge drinking, and alcohol-induced blackouts over time. We also took a relatively novel approach to the assessment of early onset drinking by using a latent construct derived from age at first drink, first high, and first drunk. This allowed us to examine early onset drinking with both objective (first drink) and subjective (first high, first drunk) measures.

Our findings indicate that early onset drinkers reported more frequent blackouts compared with those who initiated alcohol use later. It is noteworthy, and a unique contribution to the extant literature, that early onset drinkers continued to experience more frequent blackouts over time despite a decrease in their binge drinking. Thus, early onset drinking may be a marker of an underlying vulnerability towards experiencing alcohol-related consequences, specifically blackouts, which are not entirely dependent on binge drinking.

Chapter 4: Subjective Intoxication and Motivation to Change [3]

INTRODUCTION

Although heavy drinking is common among emerging adults, especially college students, some students preparing to graduate reduce their drinking, a phenomenon known as "maturing out" (Jochman & Fromme, 2010; Patrick & Schulenberg, 2011; Sher, Bartholow, & Nanda, 2001). Some suggest that this may result from decreases in quantity rather than frequency of alcohol use (Arria et al., 2016). Among many, alcohol consumption decreases as those who are transitioning out of college are tasked with conforming to adult roles (e.g., marriage, parenthood, employment) (Staff et al., 2010).

In fact, conforming to these new roles reflects emerging adults' concern for others (Arnett, 2003), and as such, role transitions during this time can influence their alcohol use. Accordingly, intrapersonal factors (e.g., conscientiousness) become more influential during emerging adulthood, which can lead to role adoption and later reductions in problematic drinking (Lee, Chassin, & MacKinnon, 2015). Because emerging adults are afforded freedom to define their lives (Arnett, 2000), emerging adulthood is a unique transitional period marked by role changes and increases and subsequent decreases in alcohol consumption (Boyd, Corbin, & Fromme, 2014).

Consequently, the importance of this transition can increase motivation to decrease one's drinking because experiencing alcohol-related consequences becomes more salient and disruptive to conforming with adult roles. Indeed, college students who experienced physical and psychological consequences, including alcohol-induced blackouts, expressed that the particular drinking episode was not worth doing (Fairlie, Ramirez, Patrick, & Lee,

[3] Marino, E. N., & Fromme, K. (2018). Alcohol-induced blackouts, subjective intoxication, and motivation to decrease drinking: Prospective examination of the transition out of college. *Addictive Behaviors, 80,* 89–94.
Elise N. Marino made the primary contribution to the conceptualization, data analysis, and writing of this study.

2016), suggesting a recognition that their drinking was problematic and may not be worth the associated consequences. Additionally, Diulio and colleagues (2014) found that personal consequences were associated with motivation to change when social problems were low, an effect that disappeared when social problems increased. Further, abuse/dependence symptoms were associated with motivation to change; however, those with the most abuse/dependence symptoms were less motivated. Nevertheless, others have also found that abuse/dependence symptoms predicted problem recognition and motivation to change (Cellucci, Krogh, & Vik, 2006; Vik, Culbertson, & Sellers, 2000). Despite emerging adulthood being a time of experimentation with alcohol, experiencing consequences has a considerable effect on producing motivation to change.

Although the relationship between many alcohol-related consequences and motivation to change among emerging adults is documented, the relationship between blackouts, one significant consequence, and motivation to change has largely gone unexamined. Whereas Fairlie and colleagues (2016) found that blackouts predicted a belief that the drinking episode was not worth doing, it is unknown whether blackouts predict motivation to decrease drinking, a possible result of expressing this regret. Examining the relationship between blackouts and motivation to decrease drinking during the transition out of college is important because for those graduating and entering marriage, parenthood, or the workforce, it may no longer be socially or professionally normative to engage in a pattern of heavy drinking that can lead to blackouts as it previously was (Substance Abuse and Mental Health Services Administration, 2017). Blacking out can also interfere with adopting new roles because it is incongruent with their emerging self-identity. In fact, blackouts have a considerable psychological impact as some drinkers describe their blackouts as frightening and emotionally stressful (Buelow & Koeppel, 1995; White et al., 2004). Ultimately, blackouts warrant further exploration if we are to expand how we

identify catalysts for expressing motivation to decrease drinking across developmental periods.

In addition to various substance use and individual (e.g., sex, FH+, early onset of drinking, etc.) risk factors that have been identified, subjective responses to alcohol are also risk factors for blackouts. Indeed, having a low level of response (LLR; e.g., needing more drinks to feel the effects during the first 5 times ever drinking) was associated with experiencing blackouts, controlling for maximum BAC (Schuckit et al., 2016a). The LLR likely contributes to blackouts because those individuals are drinking more to feel the effects. Yet, feeling greater stimulating and sedating effects of alcohol during a heavy drinking occasion was also associated with blackouts, relationships that were not mediated by estimated BAC (Wetherill & Fromme, 2009). This finding is likely operating through different mechanisms. Individuals who feel more stimulating effects are more likely to continue drinking. Additionally, drinking heavily can produce feelings of sedation once their BAC declines. Because these findings were not explained by BAC, they raise the question of whether sensitivity to subjective experiences of drinking might better explain risk for blacking out than the actual amount of alcohol consumed. Expanding upon this, other proxies for sensitivity to alcohol's effects, specifically subjective intoxication (i.e., feeling drunk), may also be a better predictor of blackouts than quantity of drinking.

Furthering our understanding of blackouts is crucial because they are prospectively associated with other significant alcohol-related consequences after controlling for alcohol consumption. These include: future alcohol-related injuries (Hingson et al., 2016; Mundt et al., 2012), social and emotional consequences (Wilhite & Fromme, 2015), overdosing, hangovers, school/work problems, engaging in illegal activities, and legal trouble (Hingson et al., 2016). Thus, blackouts are markers of problematic drinking, which may indicate the need for behavioral changes.

Studying blackouts and subjective intoxication is particularly relevant during emerging adulthood because although this period includes experimentation with alcohol, problematic drinking can be developmentally limited after adopting adult roles, a hypothesis proposed by Arnett (2005). Thus, identifying factors that predict blackouts (i.e., subjective intoxication) can inform prevention through early identification of individuals at risk (i.e., those experiencing blackouts). Intervening early may produce reductions in problematic drinking and blackouts, which may then reduce the need to make behavioral changes by the transition out of college and into adult roles.

Because blackouts produce fragmented or total memory loss for events occurring while drinking (Hartzler & Fromme, 2003b; Wetherill & Fromme, 2011; White, 2003), experiencing blackouts can be distressing (Buelow & Koeppel, 1995; White et al., 2004). With significant distress serving as a catalyst, some individuals may be motivated to change their drinking to avoid blacking out. With motivation to decrease their drinking, these individuals may make behavioral changes to conform with their new roles. If this motivation leads to behavioral changes, we would expect to see decreases in drinking.

Consequently, we had three a priori hypotheses for the current study. First, we hypothesized that greater subjective intoxication (i.e., more times feeling drunk) would increase likelihood of experiencing blackouts across time, controlling for the quantity of alcohol consumed. Second, we hypothesized that blackouts alone are sufficient to generate motivation to decrease drinking, beyond the influence of objective (quantity of drinking) and subjective intoxication. Third, we hypothesized that this motivation would lead to future decreases in quantity consumed during the transition out of college.

METHOD

Participants and Procedure

Participants were from one cohort of first-time college freshmen at a large state university in the Southwestern United States who were recruited the summer before they matriculated. The 6-year longitudinal study received Institutional Review Board approval. After providing informed consent, participants were assessed ten times: high school, biannually during Years 1-3, and annually during Years 4-6. Participants included in the current analyses (N=1,854) completed the high school survey and must have completed at least one survey during Years 4-6. See Table 6 for demographic information.

Demographic Characteristics (N = 1,854)	Mean (SD) or n (%)
Age at Year 4	21.8 (0.4)
Female	1,152 (62.1%)
Caucasian	986 (53.2%)
Asian	360 (19.4%)
Black	75 (4.0%)
Hispanic	277 (14.9%)
Other ethnicities	156 (8.4%)

Table 6. Participant demographic characteristics

Note: Demographic characteristics are consistent with the overall sample from which these data are drawn.

Measures

Demographics

Sex, age, and self-reported race were captured at the high school survey.

Motivation to Change Drinking Behavior

Participants were asked to what extent they agreed or disagreed with the following statement: "I've been thinking that I might want to decrease my alcohol consumption" (DiClemente & Hughes, 1990). Responses were coded on a 5-point Likert-type scale (1 = disagree, 2 = slightly disagree, 3 = neither, 4 = slightly agree, and 5 = agree). Motivation to change drinking behavior was assessed during Years 4-6, and we used the Likert coding in our main analyses.

Alcohol-Induced Blackouts

A single item asked participants to indicate how often during a time frame of the past three months they "had difficulty remembering things you said or did, or events that happened, while you were drinking." The response options were on a 5-point Likert-type scale (1 = never, 2 = some of the time, 3 = half of the time, 4 = most of the time, and 5 = always). Blackouts were assessed during Years 4-6. We dichotomized any experience of blackouts (yes/no) during Years 4-6 in order to characterize the differences between those who did and did not report experiencing blackouts. For our main analyses, we used the Likert coding as a continuous measure of frequency of blacking out.

Subjective Intoxication

Using an item adapted from Jackson and colleagues (2001), we assessed frequency of subjective intoxication (i.e., feeling drunk). Participants were asked to provide an open-ended numeric response to the following question: "During the last 3 months, how many times did you get drunk (not just a little high) on alcohol?" Subjective intoxication was assessed at high school and at Years 4-6.

Quantity of Alcohol Use

Using the Daily Drinking Questionnaire (DDQ; (Collins et al., 1985), quantity of alcohol use was calculated as the average number of drinks consumed on a drinking day during a typical week over the past three months. Quantity of alcohol consumption was assessed at high school and at Years 4-6.

Statistical Analysis

We tested our hypotheses using data collected during Years 4-6, which is a time when most participants were transitioning out of college and into other social roles, making this an especially sensitive time to experience consequences from heavy drinking. Using SPSS Version 18, we examined the bivariate associations of demographic variables and alcohol use between those who were included versus excluded from our analyses, as well as between those who did and did not report experiencing any blackouts (yes/no) during Years 4-6. We used chi-square tests to analyze categorical variables, and two-tailed *t*-tests to analyze continuous variables.

Next, using Mplus Version 7.2 (Muthén & Muthén, 1998), we ran a cross-lagged model to examine whether subjective intoxication predicted blackouts, whether blackouts at Year 4 predicted motivation to change at Year 5, and whether this motivation predicted less alcohol use by Year 6. This path analysis controls for the associations between variables at each year and tests the predictive power of our constructs across time. We used Maximum Likelihood estimation to account for missing data. We assessed model fit using the following indices: the chi-square goodness-of-fit test, root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker-Lewis index (TLI), and standardized root mean residual (SRMR). Because chi-square is not an especially sensitive index of model fit, CFI and TLI greater than .95, RMSEA less than .08, and SRMR less than .05 are typically used as indices of a well-fitting model (Kline, 2011).

RESULTS

Attrition Analyses

Due to missing data for all three assessment points, 391 participants from the original longitudinal sample (n = 2,245) were excluded from the current study. Based on the high school survey which all longitudinal participants completed, there were some differences between those who were included versus excluded from these analyses. Compared with those excluded from the current study (n = 391), those who were included (n = 1,854) were significantly more likely to be women (49.1% vs 62.1%, $p < .001$), to report fewer times feeling drunk (2.22 vs. 1.60, $p = .012$), and to report fewer drinks per drinking day (quantity) (2.4 vs 1.8, $p = .001$) in the past three months at the high school survey. There were no significant differences between the groups in age or self-reported race.

Participant Characteristics

Overall, 10.4% (Year 4), 9.6% (Year 5), and 9.4% (Year 6) of participants agreed or slightly agreed that they were considering decreasing their alcohol consumption. See Table 7 for frequency of motivation to change, subjective intoxication, quantity of alcohol use, and blackouts.

Participant Characteristics (N = 1,854)	Mean (SD)
Year 4 motivation to change	1.9 (1.2)
Year 5 motivation to change	1.8 (1.2)
Year 6 motivation to change	1.8 (1.2)
Year 4 frequency feeling drunk	3.5 (6.6)
Year 5 frequency feeling drunk	2.9 (5.5)
Year 6 frequency feeling drunk	2.9 (6.3)
Year 4 quantity of alcohol consumption	2.7 (2.4)
Year 5 quantity of alcohol consumption	2.5 (2.2)
Year 6 quantity of alcohol consumption	2.4 (2.6)
Year 4 blackouts	1.5 (0.7)
Year 5 blackouts	1.5 (0.7)
Year 6 blackouts	1.5 (0.7)

Table 7. Alcohol use characteristics for all participants

Note: Frequency of motivation to change, feeling drunk, quantity (i.e., drinks per drinking day), and blackouts were calculated for the previous three months at each assessment.

Altogether, 52.0% of participants reported experiencing blackouts during Years 4-6. Those who experienced any blackouts during Years 4-6 were significantly more likely to be Caucasian, express greater motivation to change, and report more times feeling drunk and greater quantity of alcohol consumption during all three years (Table 8).

Participant Characteristics (N = 1,854)	Blackouts Yes (n = 965)	Blackouts No (n = 889)	*p* value
Demographics			
Female	619 (64.1%)	533 (60.0%)	.063
Age at Year 4	21.8 (0.3)	21.8 (0.4)	.578
Caucasian	613 (63.5%)	472 (53.1%)	< .001
Alcohol Use			
Year 4 motivation to change	2.0 (1.3)	1.7 (1.1)	< .001
Year 5 motivation to change	2.0 (1.4)	1.6 (1.0)	< .001
Year 6 motivation to change	2.0 (1.3)	1.6 (1.0)	< .001
Year 4 frequency feeling drunk	5.6 (7.8)	1.1 (3.4)	< .001
Year 5 frequency feeling drunk	4.7 (6.7)	0.7 (1.9)	< .001
Year 6 frequency feeling drunk	4.7 (7.8)	0.8 (2.5)	< .001
Year 4 quantity of alcohol consumption	3.7 (2.4)	1.6 (1.9)	< .001
Year 5 quantity of alcohol consumption	3.4 (2.4)	1.5 (1.5)	< .001
Year 6 quantity of alcohol consumption	3.1 (3.1)	1.5 (1.6)	< .001

Table 8. Bivariate analyses of demographic and alcohol use characteristics by any reported blackouts during Years 4-6

Notes: n (%) or mean (SD). Frequency of motivation to change, feeling drunk, and quantity (i.e., drinks per drinking day) were calculated for the previous three months at each assessment.

Cross-Lagged Model

Finally, using Maximum Likelihood estimation, we ran a cross-lagged model across three years to examine the associations among motivation to change, blackouts,

subjective intoxication, and quantity of alcohol use (Figure 5). Because subjective intoxication and quantity were positively skewed, they were log transformed and afterwards showed no significant skew. Sex was included as a covariate, and alcohol-induced blackouts and quantity were regressed on sex at all three years. Consistent with the extant literature, women were more likely to report experiencing blackouts (p = .001), and men reported significantly greater quantity of alcohol consumption (p < .001). All variables within a given year were covaried with one another, and Year 4 variables were covaried with the corresponding variable at Year 6. All covariances among variables were statistically significant (all ps < .01). The final model demonstrated adequate fit (chi-square = 110.216, df = 18, p < .0001; RMSEA = .053, 90% CI [.043, .062]; CFI = .988; TLI = .949; SRMR = .030).

Year 4 to Year 5

In testing Hypothesis 1, subjective intoxication at Year 4 prospectively predicted blackouts at Year 5 (β=0.144, 95% CI [0.072,0.215], p<.001). In testing Hypothesis 2, blackouts at Year 4 significantly predicted motivation to change at Year 5 (β=0.094, 95% CI [0.031,0.156], p<.01). All constructs demonstrated good stability from Year 4 to Year 5 (all ps<.001).

Year 5 to Year 6

Again testing Hypothesis 1, subjective intoxication at Year 5 prospectively predicted blackouts at Year 6 (β=0.165, 95% CI [0.095,0.236], p<.001). In testing Hypothesis 3, motivation to change at Year 5 did not significantly predict a decrease in quantity of alcohol consumption by Year 6 (p=.076). In line with this, there was no significant mediation from blackouts at Year 4 through motivation to change at Year 5 to

quantity at Year 6. Again, all constructs demonstrated good stability from Year 5 to Year 6 (all *p*s<.001).

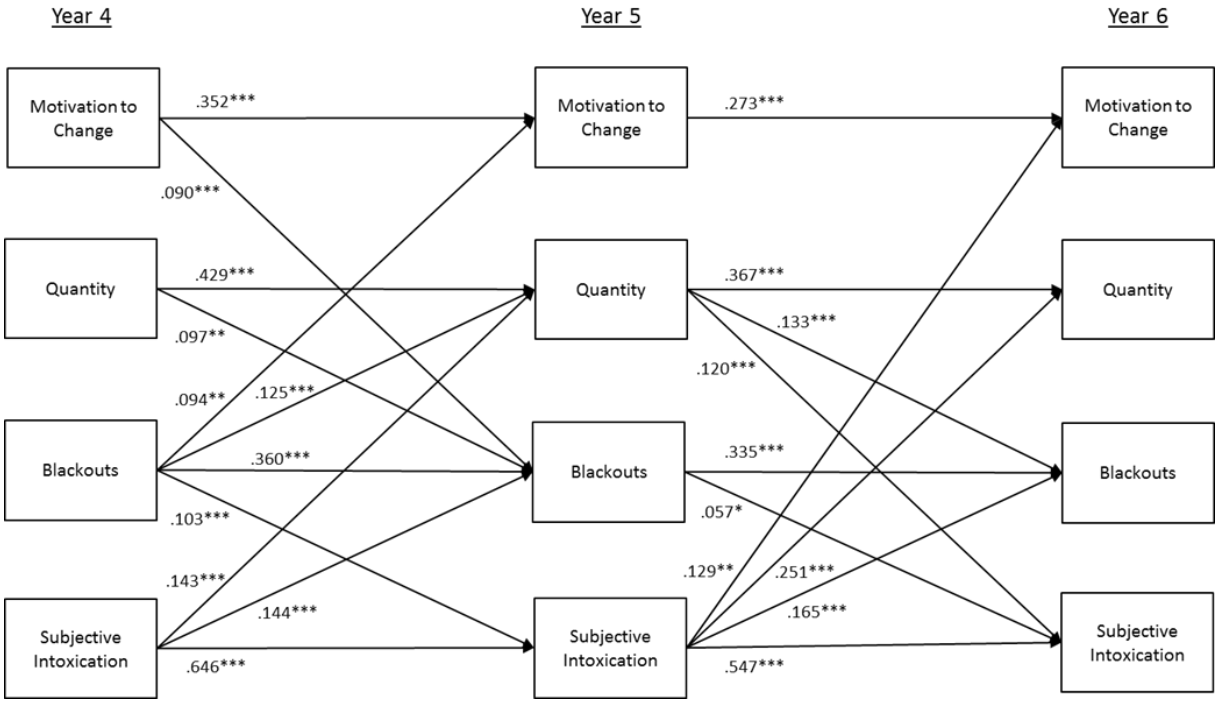

Figure 7. Cross-lagged model for motivation to change, blackouts, subjective intoxication, and alcohol consumption.

Notes: * $p < .05$, ** $p < .01$, *** $p < .001$. Only statistically significant paths are shown. Path coefficients are standardized estimates. Sex was included as a covariate, and it was regressed onto alcohol-induced blackouts and quantity at all three years.

Sensitivity Analyses

In our main analyses, we wanted to include all participants who completed assessments during Years 4-6. This included 108 individuals who reported no alcohol use, but some of whom expressed motivation to change. In order to test the power of our

findings, we ran sensitivity analyses using only those participants who reported current drinking (n = 1,746). All results from the cross-lagged model remained the same.

DISCUSSION

Our findings show mixed support for our a priori hypotheses that subjective intoxication would predict blackouts and that experiencing blackouts would predict motivation to decrease drinking, which would then predict reductions in quantity of alcohol use. Indeed, subjective intoxication prospectively predicted blackouts across both time waves, and blackouts also predicted subjective intoxication, highlighting the bidirectional relationship between these constructs. Further, experiencing blackouts prospectively predicted motivation to change from Years 4-5 but not from Years 5-6. This motivation to change, however, did not predict a significant decrease in quantity of alcohol consumed by the third year. Given this, subjective intoxication is a robust risk factor for blackouts, and blackouts are modest, developmentally-limited predictors of motivation to change as this was only true across Years 4-5. Finally, blackouts do not appear to predict behavior change among emerging adults as they transition out of college.

Our findings are consistent with prior work that subjective responses to alcohol are associated with experiencing blackouts (Schuckit et al., 2016a; Wetherill & Fromme, 2009). Having controlled for the quantity of drinking, our results suggest there is something unique about the sensitivity to feelings of intoxication that increases the likelihood of experiencing blackouts. This would be in line with the findings of Wetherill and Fromme (2009), who indicated that both environmental and genetic influences likely contribute to the effect of subjective responses to alcohol on blackouts. For instance, an environment that encourages drinking to the point of intoxication may promote a rapid rate of drinking, which produces stronger feelings of intoxication, and increases the likelihood of blacking

out (Jennison & Johnson, 1994; Perry et al., 2006; White, 2003; White et al., 2004). Additionally, those with lower tolerance to alcohol will experience stronger feelings of intoxication with the same quantity of drinking, thus increasing the likelihood of blacking out. Our finding that subjective intoxication confers risk for blackouts confirms our first a priori hypothesis.

Additionally, our second hypothesis that blackouts alone are sufficient to produce motivation to decrease drinking showed mixed findings. This effect was only found from Years 4-5, but not from Years 5-6. Even though some drinkers are distressed by their blackouts, which led some to monitor their drinking for weeks after experiencing a blackout (Buelow & Koeppel, 1995; White et al., 2004), this appears to be a time-limited phenomenon. We did not find an effect of blackouts in Year 5 on motivation to change in Year 6, perhaps because these participants had already "matured out" of heavy drinking (Wilhite & Fromme, 2015) and transitioned into adult roles. This change would reduce both the likelihood of experiencing blackouts and the motivation to further reduce their drinking. Conversely, Years 4-5 represent the preparation and early stages of entering adult roles (Boyd et al., 2014), whereas during years 5-6 those changes may have solidified. This also fits with the idea of role socialization in that during the transition out of college, individuals are first initiating changes to socialize into what is expected of them in their new roles. After that period, they may have already socialized into roles that are associated with decreased drinking.

Although results failed to support our third a priori hypothesis that motivation to change would lead to reductions in quantity, this is consistent with previous findings that college students who engage in self-change behaviors are often unsuccessful (Caldeira et al., 2009). Interestingly, some have found that in the short-term, expressing motivation to change predicted less drinking and fewer consequences one week later (Merrill, Wardell,

& Read, 2015). Because our assessments were yearly, it is possible that we missed short-term reductions in quantity of drinking among those who expressed motivation to change. It is also possible that motivation to decrease drinking was not strong enough for us to expect significant changes in drinking behavior.

Strengths and Limitations

The prospective nature of our analyses allowed us to examine blackouts, subjective intoxication, and motivation to change over time and how that influenced future drinking using robust path analyses in a large sample. Nevertheless, our sample consisted of college students, limiting the generalizability of our findings to other populations. Because our analyses focus on emerging adulthood, findings may differ in other age groups. Despite this, the highest rates of alcohol-related problems occur in this age group, making this an important developmental phase to study. We also used single items to assess blackouts, subjective intoxication, and motivation to change; however, single items have been used previously for blackouts (Schuckit et al., 2015; Schuckit et al., 2016a, 2016b), subjective intoxication (Quinn & Fromme, 2012), and motivation to change (Chung, Pajtek, & Clark, 2013; Morgenstern et al., 2016). Finally, our model only allowed us to examine three years of data because our expanded definition of blackouts was not added until the Year 4 survey. Because we are looking at predicting change over time, examining additional timepoints may have strengthened our analyses.

Conclusions and Clinical Implications

This work highlights subjective intoxication as a robust risk factor for blackouts, which may be due to environmental and individual difference factors that influence individuals' sensitivity to subjective feelings of intoxication. Further, we identified blackouts as a modest predictor of motivation to decrease drinking, beyond the effects of

objective and subjective intoxication, during the initial transition out of college but not from Years 5-6. This may be because participants may have assimilated into their roles by Years 5-6, thereby reducing their need to change; whereas, Years 4-5 represent the time to socialize into new roles when making changes is more important. Thus, this effect appears to be developmentally specific. By expressing a motivation to decrease their drinking, some individuals may have recognized that their drinking had been leading to problems, especially blackouts, which is incongruent with their efforts to conform to new adult roles. Yet, changes in drinking behavior were not identified by common markers of successful behavior change (i.e., reductions in quantity of drinking). Despite this, our work highlights the need to augment prevention programs aimed at reducing problematic alcohol use with education about blackouts and strategies for reducing their frequency.

Chapter 5: General Discussion

An in-depth examination of alcohol-induced blackouts among one cohort of emerging adults during the transition out of college identified three risk factors for these consequences after controlling for current alcohol consumption. First, after parsing the effects of maternal FH+ and paternal FH+, a maternal FH+ in men was a significant predictor of experiencing blackouts. Second, an early onset of drinking predicted a greater level of blackouts across three years during the transition out of college, but it did not predict growth or changes in the frequency of blackouts across that time. Third, subjective intoxication prospectively predicted experiencing blackouts across two consecutive time waves during the transition out of college. In addition to examining risk factors, the relationship between experiencing blackouts and being motivated to make behavioral changes was also examined. In doing so, blackouts prospectively predicted expressing a motivation to decrease drinking during the initial transition out of college; however, this motivation to change did not predict future changes in drinking behavior by the second year of the transition out of college.

Approximately 52% to 69% of emerging adults reported experiencing blackouts during the transition out of college. The higher end of this range may be attributable to stricter inclusion criteria related to the variables measuring current alcohol consumption that were examined in the statistical models in the earlier studies (e.g., binge drinking for the early onset of drinking study). Nevertheless, this confirms a differential susceptibility towards experiencing these consequences. Finding that these three markers of risk significantly predict experiencing blackouts after controlling for current alcohol consumption highlights the fact that to explain this differential susceptibility, it is necessary to examine the underlying mechanisms behind a maternal FH+, early onset of drinking,

and subjective intoxication. Thus, conceptualizing risk for blackouts is complex as it will involve many facets of both environmental and genetic influences, which together establishes a role for the interplay between environment and genetics.

DISTINCT UNDERLYING MECHANISMS: THE ROLE OF THE ENVIRONMENT

High-risk environments are associated with engaging in problematic substance use and then experiencing alcohol-related consequences, including blackouts. Examples of such environmental influences include early access to alcohol, parents having lax views on alcohol use for children, social encouragement to use alcohol, and a deviant peer group. These environmental factors can influence how a maternal FH+, early onset of drinking, and subjective intoxication confer risk for blackouts.

Because family environment is a strong predictor of alcohol use initiation, alcoholic mothers who model problematic drinking and who then provide their sons with early access to alcohol can produce a high-risk environment that will influence the initiation of alcohol consumption at an early age. In fact, mothers' alcohol use is a strong predictor of alcohol use initiation during adolescence, and it is a better predictor than tobacco or marijuana use, as well as a better predictor than fathers' substance use (Capaldi, Tiberio, Kerr, & Pears, 2016). Individuals with parents who approve of their alcohol use, in particular mothers who approve, are also more likely to experience negative consequences resulting from their drinking (Boyle & Boekeloo, 2006). This evidence suggests that there is something unique about a mother modeling and approving of drinking versus a father that ultimately places men at elevated risk for early initiation of alcohol use and alcohol-related problems. Because some mothers who are problem drinkers hide their alcohol use, in addition to environmental factors, it is likely that a maternal FH+ conferring risk for blackouts is also being driven by an inherited genetic susceptibility towards alcohol-related problems.

Adolescence is a particularly vulnerable period for developing problems resulting from the early initiation of alcohol consumption, including experiencing alcohol-induced blackouts. Once they have initiated alcohol use at an early age, adolescents may be susceptible to social pressure to drink heavily to conform with their peers' behavior. Social pressure can influence the development of a pattern of heavy drinking, which can then result in alcohol-related consequences. This pattern of drinking may persist into emerging adulthood with encouragement from a deviant peer group that also consumes alcohol. Similar to adolescence, emerging adults who face social pressure to drink heavily may be at increased risk for experiencing more alcohol-related consequences. Emerging adults with a sensitivity to feelings of intoxication who then engage in this pattern of drinking at the encouragement of deviant peers may be more likely to experience blackouts.

These high-risk environmental factors affect a trajectory of alcohol use from the initiation of alcohol consumption to the progression to heavy alcohol use to the point of intoxication. Although alcohol consumption is necessary to experience blackouts, BAC alone does not explain the occurrence of these phenomena. This suggests that the underlying mechanisms behind a maternal FH+, early onset of drinking, and subjective intoxication most likely involve more than just environmental factors, thus highlighting the necessary role of a genetic susceptibility towards experiencing blackouts.

COMMON UNDERLYING MECHANISM: THE ROLE OF GENETICS

In fact, blackouts themselves are approximately 50% heritable (Nelson et al., 2004). This suggests that there is an underlying genetic predisposition towards experiencing these consequences, and, as such, genetic factors are likely essential in explaining maternal FH+, early onset of drinking, and subjective intoxication conferring risk for blackouts. A genetic

vulnerability towards experiencing blackouts may then be the underlying mechanism that transcends all three risk factors.

Alcohol use disorder is approximately 50% heritable (Enoch & Goldman, 2001; Mbarek et al., 2015; Verhulst, Neale, & Kendler, 2015), and alcohol use initiation is approximately 40% heritable (Rhee et al., 2003; Ystrom, Kendler, & Reichborn-Kjennerud, 2014). This indicates that having a FH+ is a significant risk factor for developing alcohol use disorder, and it is also associated with initiation of alcohol consumption at an early age. Because there is substantial common genetic risk for early initiation of drinking and later development of alcohol use disorder (Agrawal et al., 2009; Richmond-Rakerd et al., 2016; Ystrom et al., 2014), a maternal FH+ and early onset of drinking may also share common inherited genetic vulnerabilities.

Similar to alcohol use disorder and early onset of drinking, subjective responses to alcohol also demonstrate significant heritability, with estimates ranging from 60% to 67% (Heath et al., 1999; Kalu et al., 2012; Viken, Rose, Morzorati, Christian, & Li, 2003). Longitudinal work demonstrated that a low level of response to alcohol among emerging adults was associated with significant risk for later developing alcohol use disorder (Schuckit, 1994; Schuckit & Smith, 1996). A low level of response to alcohol was then purported to be an underlying cause of alcohol use disorder. With this, an inherited genetic predisposition towards individual differences in subjective responses to alcohol suggests a genetic link between maternal FH+ and sensitivity to subjective feelings of intoxication.

Altogether, a maternal FH+, early onset of drinking, and subjective intoxication may, indeed, be connected by a common inherited genetic vulnerability. These three factors are intrinsically linked with one another down to a genetic level, and individuals who then inherit a genetic vulnerability are at heightened risk for experiencing blackouts. This underscores the idea that a common genetic vulnerability is likely crucial to explaining

how these three factors generate risk for blackouts, but it is unlikely that an underlying genetic mechanism is operating independent of environmental mechanisms.

CONNECTING THE UNDERLYING MECHANISMS TO EXPLAIN RISK FOR BLACKOUTS

Although environment and genetics are crucial to explaining how these three factors generate risk for blackouts, neither the environment nor genetics alone can explain the occurrence of these phenomena. Thus, a common genetic vulnerability and the presence of environmental factors may operate together for maternal FH+, early onset of drinking, and subjective intoxication to generate risk for experiencing blackouts. There could be gene-environment correlations, which suggests that there is genetic control of exposure to an environment. Gene x environment interactions are also possible; this suggests that there is environmental control of genetic expression. These gene-environment explanations demonstrate how the combination of genetic and environmental mechanisms can influence drinking outcomes (Young-Wolff, Enoch, & Prescott, 2011), including how these three factors confer risk for blackouts during emerging adulthood.

A gene-environment correlation suggests that a common inherited genetic risk can influence the extent to which individuals will be exposed to high-risk environments that together increases the likelihood that they will be susceptible to experiencing alcohol-induced blackouts. A common genetic risk for blackouts may influence whether sons will have mothers who create an environment with alcohol use being modeled and lax views on alcohol use for sons. In fact, alcohol use by parents has a modest effect on adolescents' alcohol use; although, this effect diminished with age (Poelen, Scholte, Willemsen, Boomsma, & Engels, 2007; Scholte, Poelen, Willemsen, Boomsma, & Engels, 2008). In addition to predicting adolescents' alcohol use, parents' alcohol consumption and alcohol consumption to intoxication also predicted adolescents' drinking to intoxication

(Latendresse et al., 2008). This effect remained significant after controlling for environmental factors, suggesting a genetic vulnerability towards consuming alcohol may influence the effect parents' drinking has on adolescents' decision to drink and drink to intoxication.

With peers having more influence over adolescents as they mature (Dick, 2011), peers may influence adolescents' decision to drink at an early age. Indeed, some have found that genetic factors influence the effect friends' alcohol use has on adolescents' own alcohol use (Fowler et al., 2007). This suggests that individuals are genetically vulnerable to conforming with peer behaviors. Others have also found that genetic factors, some of which were related to substance use, were associated with being exposed to a best friend who engages in heavy substance use (Harden, Hill, Turkheimer, & Emery, 2008). As such, a common inherited genetic risk towards experiencing blackouts may affect whether those individuals will then be exposed to and/or seek out peers who provide access to alcohol and who encourage those individuals to drink to the point of intoxication at an early age.

Initiating alcohol use at an early age then predisposes those individuals to develop a pattern of problematic drinking that will persist into emerging adulthood. Thus, a common genetic vulnerability may also influence the extent to which emerging adults are exposed to deviant peers who provide continued social pressure to drink to the point of intoxication. This heightens those individuals' risk for experiencing blackouts. In fact, individuals with high genetic risk for substance use disorders who associate with deviant peers that engage in heavy substance use are more likely to experience alcohol-related problems during emerging adulthood (Bountress, Chassin, & Lemery-Chalfant, 2017). Consequently, a common inherited genetic vulnerability can influence the extent to which individuals will be exposed to high-risk environments that influence the initiation of

alcohol use at an early age and progression to drinking to intoxication, which increases their likelihood of experiencing blackouts.

These proposed gene-environment correlations could be classified as active, evocative, or passive (Scarr & McCartney, 1983). An active gene-environment correlation suggests that the individual's genes influence whether he or she will select particular environments, such as seeking out peers who provide alcohol at an early age (Hill, Emery, Harden, Mendle, & Turkheimer, 2008). They may also be classified as evocative, where peers evoke certain behaviors from an individual based on the individual's genes, including consuming alcohol at a young age (Dishion & Owen, 2002; Fowler et al., 2007). These explain how peer selection is driven, in part, by genetics. The gene-environment correlations could also be classified as passive, such that the individual's parents pass on their genes and are also involved in creating a home environment. If a mother being a problem drinker creates parent-child conflict and the home environment is then conducive to early initiation of alcohol use, for example, this can influence whether those individuals will initiate alcohol use early, progress to drinking to intoxication (Latendresse et al., 2008), and then experience alcohol-related problems, including blackouts.

In contrast to this perspective, being exposed to high-risk environments may influence the extent to which a common genetic risk for blackouts in a maternal FH+, early onset of drinking, and subjective intoxication is expressed, or a gene x environment interaction. Growing up in the high-risk environment produced by a maternal FH+ may affect the expression of a shared genetic risk, which then influences alcohol consumption and related consequences. For instance, parents' permissive attitudes regarding alcohol use for sons was a significant risk factor for those men to engage in problematic alcohol use and then experience alcohol-related consequences as emerging adults (Abar, Abar, & Turrisi, 2009; Abar, 2012). Additionally, sons witnessing their mothers frequently being

drunk was associated with those sons reporting a greater frequency of being drunk themselves (Cleveland, Reavy, Mallett, Turrisi, & White, 2014). As such, parents' permissive attitudes about alcohol use for sons and mothers modeling problematic drinking can influence the expression of an inherited genetic vulnerability. Together, this affects whether those emerging adults will engage in problematic drinking and then experience alcohol-related consequences, including blackouts.

Because parents' influence over their children diminishes during adolescence (Dick, 2011), peer influences become more important as adolescents begin to mature in age. In line with this notion, some have found that the interaction between genetic factors and associating with deviant peers predicted an individual's substance use (Cooke et al., 2015; Kendler et al., 2011). More specifically, Harden and colleagues (2008) found that a best friend's substance use was the strongest predictor of an adolescent's substance use if the adolescent also had a genetic vulnerability towards using substances. Further, others have found that associating with deviant peers interacted with genetic factors to predict adolescents' alcohol use, with larger effects found for associating with increasing numbers of deviant peers (Dick et al., 2007). With this, early initiation of alcohol use and then engaging in heavy alcohol use at an early age at the direction of deviant peers may influence the expression of a common genetic risk. A genetic risk being expressed due to associating with a deviant peer group that encourages alcohol use initiation at an early age then increases the likelihood that those individuals will experience blackouts. Indeed, some have found that early onset drinkers experiencing alcohol-related problems was largely attributable to genetic factors (Agrawal et al., 2009).

After early initiation of alcohol use, social pressure to drink heavily during emerging adulthood may also influence a common inherited genetic risk being expressed. This social pressure from peers that encourages alcohol consumption to the point of

intoxication coupled with an expressed shared genetic vulnerability can increase risk for experiencing blackouts. This is consistent with evidence suggesting that the interaction between environmental factors, such as deviant peers, and genetics predicted those individuals experiencing alcohol-related problems (Kendler et al., 2011). In fact, with greater substance use by deviant peers, the influence of genetics on an individual's own pattern of alcohol use increases (Cooke et al., 2015; Dick et al., 2007; Kendler et al., 2011), and developing a problematic pattern of alcohol use can lead to alcohol-related problems, including blackouts. This suggests that environmental factors play a crucial role in the expression of genetic risk. Consequently, distinct high-risk environments influence the expression of a common inherited genetic vulnerability that together increases likelihood of experiencing alcohol-induced blackouts during emerging adulthood.

Ultimately, no single factor can explain the occurrence of blackouts. Having a maternal FH+, initiating alcohol use early, or being sensitive to subjective feelings of intoxication alone does not fully predict who will experience blackouts. With only about half of drinkers being susceptible to experiencing blackouts, the interplay between genetics and environment is necessary to explain the complex underpinnings of a maternal FH+, early onset of drinking, and subjective intoxication generating risk for blackouts. A common inherited genetic vulnerability coupled with the distinct high-risk environmental factors, put together as gene-environment correlations or gene x environment interactions, is the best way to form a complete explanation for how these three factors confer risk for experiencing alcohol-induced blackouts across emerging adulthood.

FUTURE DIRECTIONS

The field would benefit from further examination of the genetic basis of blackouts, which will help determine the extent to which genetic factors underlie maternal FH+, early

onset of drinking, and subjective intoxication. For instance, twin models could be used to analyze the amount of additive genetic variance, shared environmental variance, and non-shared environmental variance in blackouts. These variances could be regressed onto each of these three risk factors in three separate models. Then, one could correlate the amount of additive genetic variance in blackouts that exists across the models examining the three risk factors. Finding significant correlations in additive genetic variance among a maternal FH+, early onset of drinking, and subjective intoxication using this type of twin modeling would create an opportunity to confirm the hypothesis that these three risk factors share a common inherited genetic vulnerability towards experiencing blackouts.

Because blackouts are likely polygenic, genetic analyses utilizing polygenic risk scores could analyze the extent to which genetic risk for blackouts moderates and/or mediates the predictive effect of maternal FH+, early onset of drinking, and subjective intoxication on blackouts. In creating polygenic risk scores, one would first impute missing genotypes to produce two separate genetic samples with overlapping genotypes. Using the Collaborative Study on the Genetics of Alcoholism, which also includes data on blackouts, as the discovery sample, a genome wide association study could be performed to calculate genome-wide effect sizes for blackouts for each genotype in this sample. Then, using the follow-up study to the current project, which utilized the same participants, as the target sample, those effect sizes could be transferred from the discovery sample and multiplied by the risk allele frequency in each genotype for each participant in the target sample. To create polygenic risk scores for blackouts in the target sample, one would calculate the linear relationship between risk allele frequency each participant possesses and the effect sizes. This would create one beta weight, which is an observed variable, that represents the polygenic risk score for blackouts for each participant. Using this score as an observed variable of genetic risk, path analyses could be performed to examine whether the

predictive effect of these three risk factors on blackouts is mediated by the interaction between polygenic risk for blackouts and the presence of high-risk environmental factors. This would provide an opportunity to test the overarching hypothesis that both genetics and environment are necessary to explain how these individual factors confer risk for alcohol-induced blackouts.

CLINICAL IMPLICATIONS

The importance of understanding what makes certain individuals susceptible to blackouts is seen in the fact that some drinkers find blackouts distressing. This may lead them to seek treatment and make behavioral changes. Indeed, experiencing frequent blackouts does cause some drinkers to express a motivation to decrease their drinking during the first year of the transition out of college; although, this motivation did not lead to significant reductions in quantity of alcohol consumed by the second year of the transition out. It is possible that changes in drinking behavior occurred shortly after expressing this motivation to change but did not persist one year later. Thus, research examining the role of blackouts in creating behavioral changes should assess for short-term changes in drinking behavior and reductions in alcohol-related problems, which can help emerging adults recognize benefits from their efforts to change their drinking patterns. Research in this area should also consider measuring emerging adults' self-change efforts using discrete indices of successful behavior change (e.g., fewer blackouts) in addition to traditional indices (e.g., reductions in quantity of alcohol consumed). Although future changes in drinking behavior were not identified, this work highlights the motivating nature of experiencing blackouts and the need to prevent these significant negative consequences of alcohol consumption.

Because behavioral risk taking, including alcohol use, peaks in emerging adulthood, this is an important and necessary time to implement such prevention efforts to reduce problematic drinking and the likelihood of experiencing negative consequences, including alcohol-induced blackouts. These prevention efforts should involve educating the public about the risk factors for and consequences of experiencing blackouts. Popular beliefs about blackouts are often incorrect, such as the misperception that blacking out is equivalent to passing out. Thus, providing accurate and current information to the public is vital if we are to prevent these significant and distressing negative consequences of alcohol consumption. For example, college orientations for incoming freshman that include education about problematic alcohol use should also include educational information about blackouts, what puts drinkers at risk for experiencing these consequences, and how to prevent them. Although some of the factors that put drinkers at risk for experiencing blackouts are non-malleable, such as having a maternal FH+, having already initiated alcohol use at an early age, or being sensitive to subjective feelings of intoxication, being informed that these factors place them at elevated risk for experiencing blackouts may increase the likelihood that they will engage in protective behaviors to avoid experiencing blackouts.

As emerging adults are a population known for its low rates of treatment seeking, it is possible that numerous types of self-change behaviors can be learned without formal treatment. These self-change behaviors can include protective behavioral strategies, such as alternating drinks with water, sipping drinks instead of gulping, and not drinking shots. Such behavioral changes may help reduce the quantity of alcohol being consumed, which may also reduce the likelihood of experiencing blackouts. Education about blackouts and protective behavioral strategies should be incorporated in the alcohol education course colleges are already providing. This educational material should also be made available on

You Tube and other social media platforms to increase the availability and reach of this important information to the public. Implementing these prevention efforts early will give emerging adults strategies to decrease the likelihood of experiencing blackouts prior to the pivotal transition out of college, which may then facilitate their efforts to successfully socialize into their new adult roles once they graduate from college. In turn, this will help reduce the significant distress and harms associated with alcohol-induced blackouts.

CONCLUSIONS

With only about half of individuals who drink to similar levels of intoxication experiencing blackouts, explaining risk for these consequences requires examining the underlying mechanisms behind a maternal FH+, early onset of drinking, and subjective intoxication. Although drinking styles that produce high BACs, such as pregaming, playing drinking games, and drinking shots increase likelihood of experiencing blackouts, alcohol consumption alone does not explain risk for these consequences. Thus, the documented differential susceptibility underscores the fact that risk for experiencing blackouts is likely operating through both environmental and genetic mechanisms. These underlying mechanisms operating together outlines the most complete explanation for why these three markers confer risk for blackouts. Being the first to identify the distinct and common underlying mechanisms behind a maternal FH+, early onset of drinking, and subjective intoxication has demonstrated that blackouts are indeed complex, multidimensional phenomena, which are distressing enough to cause some drinkers to express a motivation to decrease their drinking. Ultimately, alcohol-induced blackouts are significant, neurobiological consequences of alcohol consumption for which our knowledge is still evolving, and thus, the phenomenology of blackouts warrants further exploration.

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