Alcohol Challenge Responses Predict Future Alcohol Use Disorder Symptoms: A 6-Year Prospective Study

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Background: Propensity for alcohol misuse may be linked to an individuals' response to alcohol. This study examined the role of alcohol response phenotypes to future drinking problems.

Methods: One hundred four young heavy social drinkers participated in a within-subject, double-blind, placebo-controlled laboratory alcohol challenge study with 6-year follow-up. Participants were examined for subjective responses before and after receiving an intoxicating dose of alcohol (.8 g/kg) or a placebo beverage, given in random order. Follow-up was conducted in 5 waves over 6 years after the sessions to assess drinking behaviors and alcohol use disorder (AUD) symptoms. Retention was high with 98% (509 of 520) of possible follow-ups completed.

Results: Greater sensitivity to alcohol, in terms of stimulation and rewarding effects (like, want more) and lower sensitivity to alcohol sedation predicted greater number of AUD symptoms through 6 years of follow-up. Cluster analyses revealed that for half the sample, increasing levels of stimulation and liking were predictors of more AUD symptoms with the other half divided between those showing like and want more and want more alone as significant predictors.

Conclusions: The findings extend previous findings and offer new empirical insights into the propensity for excessive drinking and alcohol problems. Heightened alcohol stimulation and reward sensitivity robustly predicted more alcohol use disorder symptoms over time associated with greater binge-drinking frequency. These drinking problems were maintained and progressed as these participants were entering their third decade of life, a developmental interval when continued alcohol misuse becomes more deviant.

Key Words: Alcohol response, binge drinking, differentiator model, reward sensitivity, stimulation, subjective effects, trajectory

Heavy alcohol consumption elevates the risk for many adverse consequences, including disease, injury, and premature death (1–3). Although most individuals who drink can do so without incurring problems, others experience significant difficulties. Understanding the etiology of harmful drinking and its relation to inherent brain reward pathways and processes (4) is important for early identification, prevention, and treatment. One potentially important aspect of these processes consists of individual responses to alcohol. Research has attempted to elucidate these responses and how they may play a critical role in the development and exacerbation of loss of control over alcohol consumption, problems, and consequences (5–11). Several theoretical models have been proposed to explain how an individual's response to alcohol may influence propensity to hazardous drinking. These all involve aspects of potentially rewarding and/or aversive responses to alcohol.

The low-level response model (12), the earliest of these models, posits that less sensitivity to alcohol increases risk for alcohol use disorders (AUDs). The model was developed primarily from a large longitudinal study of Schuckit and colleagues examining response to alcohol challenge. In that study, less intense alcohol responses, including subjective fatigue, stress hormone levels, and body sway increased the likelihood of subsequent alcohol abuse (AA) or alcohol dependence (AD) (9). These lower responses to alcohol were likened to a lack of inherent "brakes" that limit ethanol intake. However, this study lacked measurement of hedonic responses to alcohol.

Subsequent human data failed to support low-level responses in at-risk persons (13,14), and animal studies supported psychomotor stimulant mechanisms of drug reinforcement (15). Thus, a competing theory, the differentiator model (7), was introduced by Newlin and colleagues specifying that greater pleasurable and excitatory effects of alcohol during the ascending limb of the breath alcohol concentration (BrAC) curve, combined with lower sedative responses during the declining limb, increase risk for future AUD. The differentiator model differs from the low-level response model in that it likens alcohol response in persons at risk to having "an accelerator pedal without working brakes." We have shown that although differential limb-specific effects are evident, responses simply measured at peak BrAC were predictive of future drinking at 2 years in at-risk heavy drinkers (16) leading to our proposed modified differentiator model. Finally, the incentive sensitization model (17,18) specifies the independence of neural system changes underlying development of addiction. The model posits that repeated heavy exposure to drugs (and alcohol) over time increases the salience of drug cues and sensitizes the neural systems of alcohol reward underlying motivation (wanting) but not hedonic (liking) effects.

Support for these models has come from animal studies (19), retrospective recall of alcohol responses in humans, or cross-sectional alcohol challenge designs (6). Although important, animal models have limitations in translation to the complexity of human behaviors. In humans, measuring alcohol responses by retrospective memory of early effects may incur recall bias and attenuate the likelihood of producing sufficiently precise information (20,21). Cross-sectional alcohol challenge designs

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overcome this problem but may not elucidate the full scope of subjective alcohol responses (8,11) or how alcohol responses relate to future behavior. Therefore, combining alcohol challenge measures with longitudinal follow-up is crucial to uncovering the relationship of both positively and negatively valenced alcohol responses to future drinking behaviors and AUD symptoms over time.

We therefore established the Chicago Social Drinking Project to conduct alcohol challenge and longitudinal research. We previously showed (16) that heavy social drinkers exhibited higher alcohol stimulation and reward (liking, wanting) and lower sedation compared with light drinker controls, and that these alcohol responses predicted future binge-drinking behaviors through intensive 2-year follow up (16). This 2-year period provided the first prospective information on drinking relative to baseline stimulation and sedation and formed the basis for the modified differentiator model. However, because most participants were then in their 20s, we were not able to examine the important transitional period between this decade of life and ages 30 and older, when the prevalence of binge drinking, drinking problems, and AUD declines sharply for many, but not all, individuals (22,23). This transitional period is a crucial developmental life-stage interval to fully test the modified differentiator model because those who do not reduce binge drinking by this phase may be at risk for chronic drinking problems and AUD symptoms, from which much physical morbidity and psychosocial impairment occurs.

Accordingly, an extensive, repeated-measure longitudinal follow-up of this sample was extended through 6 years after the original baseline placebo-controlled alcohol challenge. In this unique long-term follow-up, the main questions examined were as follows: 1) Do alcohol responses (stimulating, rewarding, and sedative) measured in the well-controlled laboratory predict the likelihood of meeting symptoms of AUD and frequency of binge drinking over a 6-year interval after the challenge? 2) Are there individual differences or subgroups evident in the predictive relationship of alcohol response to future drinking?

Methods and Materials

The study was approved by the University of Chicago Institutional Review Board. The design was a double-blinded, placebo-controlled, within-subjects study of responses to alcohol challenge, with longitudinal follow-up of alcohol drinking behaviors and problems in 190 non-alcohol-dependent social drinkers. The laboratory phase (March 2004 to July 2006) included three sessions. After laboratory testing, each participant entered the longitudinal follow-up phase, with no participants lost to follow-up. Follow-ups were conducted from March 2005 to October 2012, at the end of years 1, 2, 4, 5, and 6 after laboratory challenge. In this report, we focus on the 104 nonalcoholic, heavy social drinkers in the sample who met inclusion criteria (consume five or more drinks for men [four for women] on an occasion one to five times per week as their predominant adult pattern [i.e., at least the past 2 years], with at least 10 but no more than 40 standard drinks weekly). The binge criteria were consistent with Substance Abuse & Mental Health Services Administration and National Institute on Alcohol Abuse and Alcoholism guidelines (24,25); the weekly consumption criteria assured overall regular alcohol exposure (26).

The 86 light drinkers in the original sample (i.e., those who consumed <6 drinks weekly with no/rare bingeing) are not described in this report because they continued with largely low-risk drinking through follow-up, averaging 1.7 $\pm$ .07 SEM drinking days per week, 1.8 $\pm$ .07 drinks per drinking day, and 3.1 $\pm$ .6 binge occasions per year. They showed primarily sedative alcohol responses (16), and no alcohol response factor predicted their future drinking behaviors or problems because there was little signal or variability in target behavior to detect.

Eligibility and Screening

Participants were recruited from advertisement and screened for these eligibility criteria: aged 21 to 35 years, weight 110 to 210 pounds, meeting heavy drinking criteria, and good general health with no current or past major medical or Axis I psychiatric disorders, including alcohol and drug dependence (excluding nicotine). Screening measures included Alcohol Quantity—Frequency (27), Timeline Follow-Back (28), the Alcohol Use Disorders Identification Test (AUDIT) (29), and a modified Structured Diagnostic Interview for DSM-IV (SCID) (30) with the screening modules for major psychiatric disorders and the full lifetime modules for AA and AD. Standard cutoff thresholds were used to rule out persons with psychiatric comorbidities, and candidates could not be taking centrally acting medications. Screening also included a brief physical examination, urine toxicology, and a blood sample for complete blood count and liver function panels. Candidates with a positive breathalyzer or urine toxicology screen (cocaine, opiates, benzodiazepines, amphetamines, barbiturates, and phencyclidine), a positive pregnancy test (women), or an abnormal blood chemistry or hepatic panel result ($\geq$2 SD above mean) were excluded. Biological family history of AUD, a risk factor in development of AUD, was not an inclusion criterion but ascertained after enrollment through a family history tree and Research Diagnostic Criteria for alcohol consequences (31) to confirm likelihood of AUD in identified relatives. Positive family history (FH) was defined as having at least one primary relative or two or more secondary relatives with AUD, and negative FH was defined as having no AUD in the previous two generations. Twenty-three participants (22%) either did not meet these criteria or were unsure about family members, so they were not classified.

Laboratory Sessions

In the individual laboratory sessions separated by at least 48 hours, participants ingested a beverage given in random order that contained a high alcohol dose (.8 g/kg alcohol) or a placebo (.0 g/kg; 1% volume of ethanol as taste mask). Another session was conducted with .4 g/kg alcohol, but this dose was subthreshold to produce subjective changes (16) and not included in this study. Doses for women were 85% of those of men to adjust for sex differences in total body water (32). To reduce alcohol expectancy, the Alternative Substance Paradigm (33) was used, with instructions that the beverage might include alcohol, a stimulant, a sedative, a placebo, or a combination of these substances. All beverages contained water, flavored drink mix, a sucralose-based sugar substitute, and the applicable dose of 190-proof ethanol. The beverage was divided into two equal portions in clear-lidded cups. Each portion was consumed within 5 minutes with a 5-minute rest interval between portions. The sessions commenced between 3:00 and 5:00 PM and proceeded for 4.5 to 5 hours in comfortable, living room–like laboratory testing rooms. Each session began with self-report assessments of abstinence compliance of 48 hours for alcohol and drugs, and 3 hours for food, caffeine, and smoking. A urine sample was collected for a random drug toxicology screen before at least one session. For women, a urine sample was collected before every session to test for HcG to verify nonpregnancy. After these compliance measures, the