ORIGINAL ARTICLE

# Rewarding, Stimulant, and Sedative Alcohol Responses and Relationship to Future Binge Drinking

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**Context:** Excessive consumption of alcohol is a major problem in the United States and abroad. Despite many years of study, it is unclear why some individuals drink alcohol excessively while others do not. It has been postulated that either lower or greater acute responses to alcohol, or both, depending on the limb of the breath alcohol concentration curve, contribute to propensity for alcohol misuse.

**Objective:** To prospectively assess the relationship of acute alcohol responses to future binge drinking.

**Design:** Within-subject, double-blind, placebo-controlled, multidose laboratory alcohol challenge study with intensive follow-up. Each participant completed 3 randomized sessions examining responses to a high (0.8 g/kg) and low (0.4 g/kg) alcohol dose and placebo, followed by quarterly assessments for 2 years examining drinking behaviors and alcohol diagnoses.

**Setting:** Participants recruited from the community.

**Participants:** High-risk heavy social drinkers aged 21 to 35 years who habitually engage in weekly binge drinking (n=104) and light drinker controls (n=86).

**Intervention:** We conducted 570 laboratory sessions with a subsequent 99.1% follow-up (1506 of 1520).

**Main Outcome Measures:** Biphasic Alcohol Effects Scale, Drug Effects Questionnaire, cortisol response, Timeline Follow-Back, Drinker Inventory of Consequences–Recent, and *DSM-IV* alcohol abuse and dependence.

**Results:** Alcohol produced greater stimulant and rewarding (liking and wanting) responses and lower sedative and cortisol responses in heavy vs light drinkers. Among the heavy drinkers, greater positive effects and lower sedative effects after alcohol consumption predicted increased binge drinking frequency during follow-up. In turn, greater frequency of binge drinking during follow-up was associated with greater likelihood of meeting diagnostic criteria for alcohol abuse and dependence.

**Conclusions:** The widely held *low level response theory* and *differentiator model* should be revised: in high-risk drinkers, stimulant and rewarding alcohol responses even at peak breath alcohol concentrations are important predictors of future alcohol problems.

**Trial Registration::** clinicaltrials.gov Identifier: NCT00961792

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HEAVY ALCOHOL DRINKING is a serious problem in young adults,[1-3] and the personal, physical, familial, and financial consequences of this excessive use are enormous. Excessive drinking is the third leading preventable cause of death in the United States,[4] and the cost of ethanol-related health care, loss of productivity, crime, and accidents totals more than $184 billion annually.[5] However, it is unclear why some individuals escalate their consumption of alcohol over time to excessive levels while others do not. A greater understanding of the factors that contribute to the escalation and maintenance of heavy drinking, especially in young adults, is essential to guide prevention, public education, and early intervention strategies for alcohol use disorders.

One potential predictor of vulnerability to alcohol use problems is the quality and magnitude of one's acute response to alcohol.[6-8] For example, a widely cited series of studies indicates that individuals with a positive biological family history (FH) of alcoholism, who are known to be at increased risk for developing alcohol dependence,[9,10] have lower responses to alcohol on several measures, including subjective alcohol intoxication ratings, body sway, stress hormones, and evoked potential responses, relative to those with a

negative FH.[11-16] In turn, even without regard to FH, lower level response to alcohol predicted the development of a future alcohol use disorder.[8] These findings have been cited as support for the *low-level response theory* articulated by Schuckit,[17] which posits that less intense alcohol responses may be associated with insensitivity to internal cues and warning signs to stop drinking, resulting in excessive consumption. This seminal work supports the idea that responses to an acute dose of alcohol may predict future drinking behaviors, above and beyond other personal risk factors such as FH.

However, there is also evidence inconsistent with the low-level response theory, suggesting instead that individuals with a FH of alcoholism or frequent heavy drinking experience *greater* alcohol-induced positive-like subjective and objective effects.[7,18-25] To resolve this apparent inconsistency, Newlin and Thomson[6] proposed the *differentiator model,* which posits that high-risk persons have greater stimulant-like effects from alcohol during the early portion of a drinking episode, when breath alcohol concentrations (BrAC) are rising, and less sedative-like effects when BrAC are decreasing. Thus, the low-level response theory proposed by Schuckit[17] may be based primarily on sedative or impairing effects during descending BrAC. Although there has been initial support for the differentiator model[7] and although stimulant responses to alcohol may lead to greater acute alcohol consumption,[26-30] thus far studies have been limited by modest sample sizes and cross-sectional designs. In fact, the only longitudinal study examining the role of acute alcohol responses to future drinking problems was conducted more than 15 years ago by Schuckit and Smith,[8] and the alcohol responses measured were primarily negative intoxicating effects.

Besides FH,[9,31] there are other risk factors for the development of alcohol use disorders, including early age onset of drinking or first intoxication[1,32,33] and frequent early adult "binge" drinking[34]—ie, consuming 5 or more drinks on 1 occasion for men, 4 or more for women.[35] In terms of the latter, habitual binge drinking during adolescence and young adulthood is highly prevalent in the United States and represents a hazardous and harmful behavior in and of itself.[3,36-38] For reasons that are not understood, some young adult binge drinkers progress to become problem drinkers, whereas others reduce their consumption during middle and later adulthood.[39-46] Among a sample of primarily young, white, male alcohol abusers, Hasin and colleagues[47] showed that several years after an initial assessment, 46% remitted and no longer met criteria for an alcohol use disorder, whereas 24% continued with alcohol abuse and 30% progressed to alcohol dependence. Preliminary cross-sectional studies[19-21] have shown that young adult binge drinkers exhibit quantitatively and qualitatively different alcohol responses than lighter drinkers. However, a key unanswered question is whether positively or negatively valenced alcohol responses *predict* subsequent drinking trajectories and alcohol problems over time.

The present study was a within-subject, double-blind, placebo-controlled, dose-ranging alcohol challenge procedure followed by a longitudinal follow-up of alcohol drinking behaviors in high-risk young adult heavy social drinkers compared with controls who were light social drinkers. The first goal was to determine whether the groups differed on subjective and objective responses to alcohol using measures sensitive to acute positive and sedative effects across the BrAC curve. The second goal was to determine whether acute alcohol responses predicted subsequent drinking patterns and alcohol-related diagnoses during a 2-year follow-up interval in each of the groups. This design provided a systematic evaluation of the low-level response model and differentiator model in the etiology of alcohol use disorders.

## METHODS

### PARTICIPANTS

The Chicago Social Drinking Project was approved by The University of Chicago Institutional Review Board, and all participants provided written informed consent. Of the initial 196 participants who attended at least 1 laboratory session, 190 completed all 3 sessions and therefore comprised the sample for the study. Laboratory sessions were conducted from March 2004 to July 2006, with all follow-ups completed by July 2008. Inclusion criteria were age 21 to 35 years; a body mass index (calculated as weight in kilograms divided by height in meters squared) of 19 to 30; good general health with no current or past major medical or psychiatric disorders, including alcohol and substance dependence; and no current medications that would interact with study procedures. Participants were selected to belong to 1 of 2 distinct drinking groups on the basis of established guidelines for heavy/binge and light drinking[3,35,48] and to be consistent with prior studies.[21,49-51] These groups were heavy drinkers (HD; n=104 [44 women]) and light drinkers (LD; n=86 [41 women]). Criteria for the HD group were (1) consuming at least 10 but no more than 40 standard alcoholic drinks per week and (2) engaging in regular binge drinking, defined as consuming 5 or more drinks on an occasion (≥4 for women) 1 to 5 times on average per week as their predominant adult pattern. Criteria for the LD group were (1) consuming at least 1 but no more than 5 standard alcoholic drinks per week and (2) engaging in infrequent binge drinking—ie, 5 or fewer times per year, but allowing for 1 past interval of a maximum of 6 months' duration of up to twice-weekly binge drinking (ie, typically during college-aged years). All attempts were made to match the groups on age as well as sex and race.

### SCREENING AND EXPERIMENTAL PROCEDURES

Participants were recruited through advertisements in local media, on Internet Web sites, by flyers, and by word-of-mouth referrals. In-person screening included administration of the Alcohol Quantity-Frequency[52] and Timeline Follow-Back[53,54] interviews to assess alcohol drinking patterns during the past 3 to 6 months. In addition, the screening portion included self-report questionnaires, including the Alcohol Use Disorders Identification Test,[55,56] the Beck Depression Inventory,[57] and the Spielberger State-Trait Anxiety Inventory.[58] Participants took part in a modified Structured Clinical Interview for *DSM-IV* Axis 1 Disorders–Patient Edition[59] that included the screening module and specific modules for mood episodes and substance use disorders, as well as a brief physical examination and urine and blood testing. Exclusion criteria were history of major Axis I

psychiatric conditions, including alcohol or substance dependence (excluding nicotine), abnormal blood chemistry or hepatic panel results (≥2 SD above the mean), positive breathalyzer or urine toxicology screen (cocaine, opiates, benzodiazepines, amphetamines, barbiturates, and phencyclidine), or positive pregnancy test. Recreational marijuana use was allowed, provided it was used no more than 3 times weekly. Participants also completed a 2-generational FH tree for alcohol use disorders and an interview of FH Research Diagnostic Criteria for drinking consequences.[60] The term *FH positive* was defined as having at least 1 primary biological relative, or 2 or more secondary biological relatives, with an alcohol use disorder, and *FH negative* was defined as having no biological relatives in the past 2 generations with an alcohol use disorder. The 45 participants with either uncertain or intermediate FH were not included in analyses pertaining to FH. Participants also completed the Sensation Seeking Scale–Form V.[61] As in other studies,[62] we modified the disinhibition subscale to remove 3 of the 10 items pertaining to behavior associated with excessive alcohol drinking or partying.

## PHASE 1: LABORATORY SESSIONS

The first phase of the study consisted of 3 randomized 5-hour laboratory sessions, each beginning between 3 and 5 PM. Subjects were tested individually, and sessions were conducted in a comfortable room and separated by at least 48 hours. Women were examined regardless of menstrual cycle phase because acute alcohol responses do not vary by menstrual phase.[63] To reduce potential alcohol expectancies, participants were told that they might receive a beverage containing alcohol, a stimulant, a sedative, a placebo, or a combination of these substances. Participants were randomized to dose order and tested under double-blind conditions. In each session, they ingested a beverage containing placebo (0.0 g/kg; 1% volume of ethanol as taste mask), a low alcohol dose (0.4 g/kg), or a high alcohol dose (0.8 g/kg). The beverage was administered in clear plastic-lidded cups in 2 equal portions that were each consumed during a 5-minute interval and separated by a 5-minute interim rest. The beverages contained 190-proof ethanol prepared with water, flavored drink mix, and a sucralose-based sugar substitute. The mean total beverage volume was 471 mL (range, 327-668 mL), and doses for women were 85% of those of men to adjust for sex differences in total body water.[64,65]

Upon arrival, the participant completed a questionnaire to confirm compliance with 48-hour drug and alcohol abstinence instructions and 3-hour abstinence from food, caffeine, and smoking. Participants underwent several objective tests to verify compliance with pretesting instructions; these tests included carbon monoxide (<10 ppm) and alcohol breathalyzer tests and, before at least 1 session, a urine toxicology screen. Women also undertook a urinary human chorionic gonadotropin test to verify nonpregnancy before each session. After these tests, the participant consumed a low-fat snack at 20% of daily kilocalorie needs, based on a macronutrient distribution of 55% of kilocalories from carbohydrates, 10% from protein, and 35% from fat.[66]

Forty-five minutes after arrival, the participant completed baseline subjective and objective measures and then consumed his or her study beverage over 15 minutes (5 minutes for each portion separated by a 5-minute rest interval) in the presence of the research assistant.[21,50,67] Subjective and objective measures were repeated during the ascending limb to the estimated peak BrAC (30 and 60 minutes, respectively, after beverage initiation) and the descending limb and alcohol elimination phase (120 and 180 minutes). The breathalyzer (AlcoSensor IV; Intoximeter, St Louis, Missouri) was programmed to display readings of 0.000 mg/dL, with the actual levels later downloaded to a computer by a separate assistant. Between time points, to circumvent potential boredom, the participant was permitted to view movies or read magazines provided by the study in a comfortable, living room–like laboratory testing room. At the end of each session, when the BrAC was 0.04 mg/L (0.04%) or lower, the participant was transported home by a car service to ensure safety. At the end of the third session, the participant was debriefed and received instructions and schedule information for the follow-up phase. Participants received a $200 check for participation in the first phase ($50 per session and a $50 bonus for completing all 3 sessions).

## SUBJECTIVE EFFECTS

Repeated assessments of subjective states by the Biphasic Alcohol Effects Scale[68] and the Drug Effects Questionnaire[69] comprised the main dependent subjective measures. The Biphasic Alcohol Effects Scale has shown good reliability and validity and yields 2 subscales, stimulation and sedation, shown to correspond to alcohol effects often observed on ascending and descending BrAC, respectively.[68] As validated in a previous report,[70] we modified the original Biphasic Alcohol Effects Scale instructions so as not to divulge beverage contents, and we administered the scale at predrink baseline. The Drug Effects Questionnaire consisted of 100-mm visual analog scales for the following postbeverage ratings: *feel drug:* "do you feel any drug effects?"; *like:* "do you like the effects you are feeling now?"; and *want more*: "would you like more of what you consumed, right now?"

## OBJECTIVE EFFECTS

Saliva samples for cortisol determination were also collected at each time point using a cotton Salivette (Sarstedt AG & Company, Nümbrecht, Germany). Samples were stored in a –80°C freezer and assayed using a high-sensitivity enzyme immunoassay kit that was standardized and validated at The University of Chicago Clinical Research Center Core Laboratory. The inter- and intra-assay coefficients of variation were 6.88% and 7.12%, respectively. Other measures (eg, psychomotor performance and eye movements) were also obtained in the sessions, and these data are reported elsewhere.[67,71-74]

## PHASE 2: FOLLOW-UP

The second phase of the study was a 2-year follow-up interval. After completion of the laboratory phase, participants were scheduled for 8 quarterly follow-ups to assess alcohol use patterns. The main dependent measure was frequency of binge drinking, defined as the percentage of days in the past month when the participant consumed at least 5 alcoholic drinks (4 for women). Binge frequency and other drinking variables (typical quantity, frequency of any drinking, and maximum quantity) were based on the Timeline Follow-Back for the 4 previous Monday-to-Sunday weeks. At 12 and 24 months, the Alcohol Use Disorders Identification Test, the Drinker Inventory of Consequences–Recent,[75] and Structured Clinical Interview for *DSM-IV* Axis 1 Disorders–Patient Edition modules for past-year alcohol abuse and dependence were also administered. Participants were compensated with $10 gift cards for each quarterly follow-up and $40 gift cards for the annual follow-ups. They also received $10 to $20 gift card incentives if they completed their follow-ups in a timely manner.

## STATISTICAL ANALYSIS

Demographic and drinking characteristics for the groups were examined by *t* tests and $\chi^2$ tests, as appropriate. Experimental

**Table 1. Participant Characteristics**

| Baseline General Characteristic | Drinkers[a] Light (n=86) | Drinkers[a] Heavy (n=104) |
|---|---|---|
| Age, y | 26.08 (0.37) | 25.28 (0.30) |
| Educational level, y | 16.66 (0.22) | 15.70 (0.14)[g] |
| White race, No. (%)[b] | 56 (65.1) | 80 (77.9) |
| Male sex, No. (%) | 44 (51.2) | 61 (58.7) |
| Spielberger trait anxiety (T score) | 44.67 (0.71) | 45.05 (0.70) |
| Beck Depression Inventory | 2.17 (0.28) | 2.87 (0.29) |
| Disinhibition scale[c] | 3.28 (0.21) | 4.95 (0.14)[g] |
| Family history positive for alcohol use disorder, No. (%)[d] | 32 (37.2) | 43 (41.3) |
| Baseline alcohol-related variables[e] | | |
| Age at first alcoholic drink, y | 17.47 (0.26) | 15.00 (0.23)[h] |
| AUDIT score | 3.27 (0.13) | 11.60 (0.36)[g] |
| No. of drinking days per month | 6.41 (0.34) | 14.22 (0.52)[g] |
| No. of standard drinks per drinking day | 1.69 (0.05) | 5.44 (0.32)[g] |
| No. of binge days per month[f] | 0.12 (0.03) | 7.90 (0.33)[g] |
| Maximum No. of drinks consumed on 1 occasion | 2.66 (0.12) | 9.96 (0.45)[g] |
| Baseline liver enzyme levels, U/L | | |
| AST | 21.4 (0.63) | 23.1 (1.05) |
| ALT | 20.7 (1.34) | 22.6 (1.80) |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUDIT, Alcohol Use Disorders Identification Test.

SI conversion factor: To convert AST and ALT to microkatal per liter, multiply by 0.0167.

[a] Data are given as mean (SEM) unless otherwise noted.

[b] Race was provided by participants among a list of options consistent with National Institutes of Health classifications.

[c] Disinhibition from the Sensation Seeking Scale, modified by removing the 3 (of 10) items that pertain specifically to alcohol.

[d] Defined as having 1 biological primary or 2 or more biological secondary relatives with an alcohol use disorder.

[e] Drink based on standard definition of 1 drink equaling 12 oz of beer, 5 oz of wine, or 1.5 oz of liquor, and monthly average taken from Timeline Follow-Back Interview for the month preceding study enrollment.

[f] Defined as 5 or more drinks per occasion for men and 4 or more drinks for women.

[g] $P < .01$.

[h] $P < .001$.

session data raw scores were analyzed by a series of 2 group × 3 dose × 5 time repeated-measures analyses of variance. Analyses were then repeated controlling for sociodemographic risk factors associated with alcohol misuse, including sex, race (white vs nonwhite), FH (positive or negative), educational level, and disinhibited personality.[36,39,43,46,76-78]

To examine the relationship of subjective alcohol response (stimulation, like, want more, and sedation) to future drinking, change scores for these 4 responses were calculated as follows: (high dose [60-minute – baseline] – placebo [60-minute – baseline]). The main calculations were based on scores at 60 minutes (peak BrAC) and for the high dose because this time point and dose level produced consistent changes on study measures and represent clinically relevant BrAC levels, ie, the US legal limit for intoxicated driving. Change scores for the low dose at peak BrAC were also examined to determine whether there were threshold effects. In addition, change scores for ascending (15-minute) and descending (120-minute) BrAC limbs were used to examine the differentiator model in detail. For objective alcohol response (cortisol), the 180-minute time point was used in the change score calculation because this interval corresponded with the peak cortisol levels and the delay in detecting levels in saliva.[79]

Participants were classified into different drinking trajectory groups on the basis of their frequency of binge drinking during the follow-up interval, using a discrete mixture modeling approach, with the number of trajectory groups determined by the Bayesian Information Criterion for model selection.[80] Linear trend analyses[81] were conducted separately for the light drinking and heavy drinking groups to examine the relationship of alcohol response change scores to the drinking trajectory groups. These analyses controlled for the main sociodemographic risk factors associated with alcohol misuse by including them as covariates. Finally, the association of each participant's alcohol responses to quarterly frequency of subsequent binge drinking was examined using a generalized estimation equations modeling approach[82] with alcohol response score, measurement time, and their interaction as covariates. The analysis used a logit link function because of the binomial distribution of binge drinking frequency. Composite generalized estimation equations models were then conducted to examine the effects of each response after controlling for the other significant responses. Given the low frequency of binge drinking among LD, generalized estimation equations analysis using any drinking frequency as the outcome was also conducted. Finally, mediational analysis[83] was conducted to examine whether the binge drinking pattern during follow-up mediated the relationship between the alcohol responses and *DSM-IV* alcohol use disorder diagnoses (alcohol abuse and dependence).

## RESULTS

### OVERVIEW

The groups were similar on most demographic characteristics (**Table 1**). As expected, the HD were higher than the LD on alcohol drinking and related variables, but liver enzyme levels did not differ between groups. The HD also had fewer years of education and higher disinhibited personality trait scores than the LD, both of which were included as covariates in all analyses. In the laboratory sessions, the BrAC changes over time confirmed the expected pattern of ascending and descending limbs. Although the HD exhibited higher BrAC at the high dose than did the LD (group×dose×time: $F_{5,940}=3.43$; $P<.01$; **Figure 1**A), the difference between groups was small (range, 0.001-0.008 mg/L at various time points), and covarying for BrAC did not alter the main findings.

### ALCOHOL RESPONSE: HD VS LD

Alcohol dose-dependently increased self-report ratings of feel drug (Figure 1B), with the LD more sensitive than the HD at the high dose of alcohol (group×dose×time: $F_{6,1128}=4.57$; $P<.001$). However, the groups differed markedly in the nature of their alcohol responses. The HD reported greater positive and rewarding subjective effects of alcohol than the LD, particularly at the high dose (**Figure 2**A-C). High-dose alcohol significantly increased Biphasic Alcohol Effects Scale stimulation ratings in the HD vs the LD during the early, ascending limb of the BrAC (group×dose×time: $F_{8,1504}=3.21$; $P=.001$) and both like and want more ratings throughout both limbs (group×dose: *like,* $F_{2,376}=15.68$; $P<.001$; and *want more,* $F_{2,376}=12.04$; $P<.001$). Furthermore, the low dose of alcohol also increased ratings for like and want more in the HD vs the LD (Figure 2).

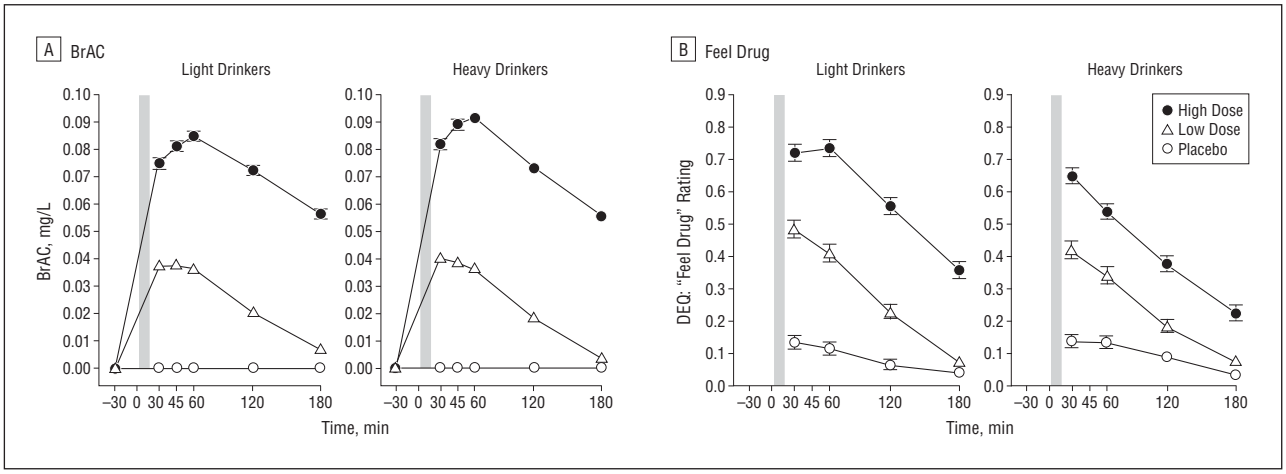


**Figure 1.** Heavy and light drinkers' breath alcohol concentrations (BrAC) (A) and Drug Effects Questionnaire (DEQ; range, 0.0-1.0) feel drug ratings (B) during the sessions. For feel drug, light drinkers had higher ratings during the high dose than did heavy drinkers at all time points; $P<.001$. The shaded bar indicates the alcohol drinking interval from time 0 to 15 minutes. Error bars indicate standard error.

Increases in Biphasic Alcohol Effects Scale sedation were noted in both groups after alcohol consumption, with the LD reporting higher sedation than the HD throughout both BrAC limbs after the high dose (group×dose×time: $F_{8,1504}=4.87$; $P<.001$; **Figure 3**A). Sedation also increased after the low dose, albeit to a lesser extent than with the high dose, with higher ratings in the LD vs the HD at peak BrAC. Increases in salivary cortisol levels were evident in the LD during the descending limb after the high dose, but there were no cortisol increases in the HD (group×dose×time: $F_{8,1504}=6.03$; $P<.001$; Figure 3B). Session order did not affect the main results ($F \geq 3.20$ for all; $P < .001$ for all). The magnitude of the group differences on alcohol response change scores was moderate, with effect sizes computed by Cohen's *d* equaling 0.47 for stimulation, 0.46 for like, 0.53 for want more, 0.53 for sedation, and 0.36 for cortisol.

The aforementioned differences between the HD and the LD on stimulation, like, want more, sedation, and cortisol remained significant after controlling for sex, race, educational level, FH, and disinhibited personality. There were no significant effects of FH of alcoholism ($F \leq 1.27$ for all; $P \geq .27$ for all) or interactions of FH and drinking group ($F \leq 1.25$ for all; $P \geq .26$ for all) or FH and sex ($F \leq 0.93$ for all; $P \geq .47$ for all) on alcohol response measures. Exploratory analyses examining a narrower criterion for FH—ie, men with alcoholic fathers (n=14) vs men with negative FH (n=44)—also were not significant for most alcohol response measures, including stimulation, sedation, like, and cortisol ($F \leq 1.06$ for all; $P > .39$ for all). However, there was a trend for an interaction in these men in ratings for want more (FH×dose×time, $F=2.03$, $P=.06$), which was driven by higher ratings during placebo for men with positive FH vs men with negative FH.

## DRINKING BEHAVIORS DURING THE FOLLOW-UP INTERVAL

Retention rates were very high in this study, with 1506 of a possible 1520 quarterly follow-ups (99.1%) completed. One male LD withdrew from the study without specifying the reason during the second year of follow-up. No other participants withdrew or were lost to contact during the 2-year interval. We imputed missing data (0.9%) by taking the average of values from the 2 surrounding follow-ups or the last observation carried forward, as warranted. During the 2 years of follow-up, drinking rates remained significantly different between the groups: LD consumed alcohol on 23% (range, 2%-62%) of days, whereas the HD consumed alcohol on 46% (range, 9%-89%) of days ($P<.001$), and LD engaged in binge drinking on 1.4% (range, 0%-8%) of days compared with 26% (range, 3%-54%) of days for HD ($P<.001$).

Quarterly follow-ups revealed that 4 trajectory patterns best described the binge drinking patterns among HD and 2 patterns best described the LD (**Table 2**). **Figure 4** depicts the 2 trajectory groups for LD: nonbinge (81.4%) and infrequent binge (18.6%) and, consistent with other studies,[46,84-87] the 4 trajectory groups for HD: exacerbating binge (6.7%), high-frequency binge (25.0%), moderate-frequency binge (59.6%), and gradual maturing binge (8.7%). The distinction of these trajectory groups was supported by other alcohol-related outcomes during follow-up, including typical and maximal drinking quantity, alcohol-related consequences, and *DSM-IV* diagnoses of alcohol abuse and dependence (**Table 3**).

## RELATIONSHIP OF ALCOHOL RESPONSE TO SUBSEQUENT DRINKING BEHAVIORS

In LD, none of the alcohol response measures (peak BrAC change scores at high dose or low dose) predicted trajectory group, binge, or any drinking outcome during the follow-up. For HD at the high dose, greater ratings of like ($r=+0.37$; $P<.001$) and want more ($r=+0.38$; $P<.001$) and lower ratings of sedation ($r=-0.20$; $P<.05$) were significantly linearly associated with subsequent drinking trajectory group, indicating an overall moderate effect (**Figure 5**). Ratings at the low alcohol dose for like ($r=+0.24$; $P<.05$) and want more ($r=+0.23$; $P<.05$) were also predictive of drinking trajectory group, but the association was weaker than for the high dose. Cortisol response for either high or low dose did not predict drinking behavior.

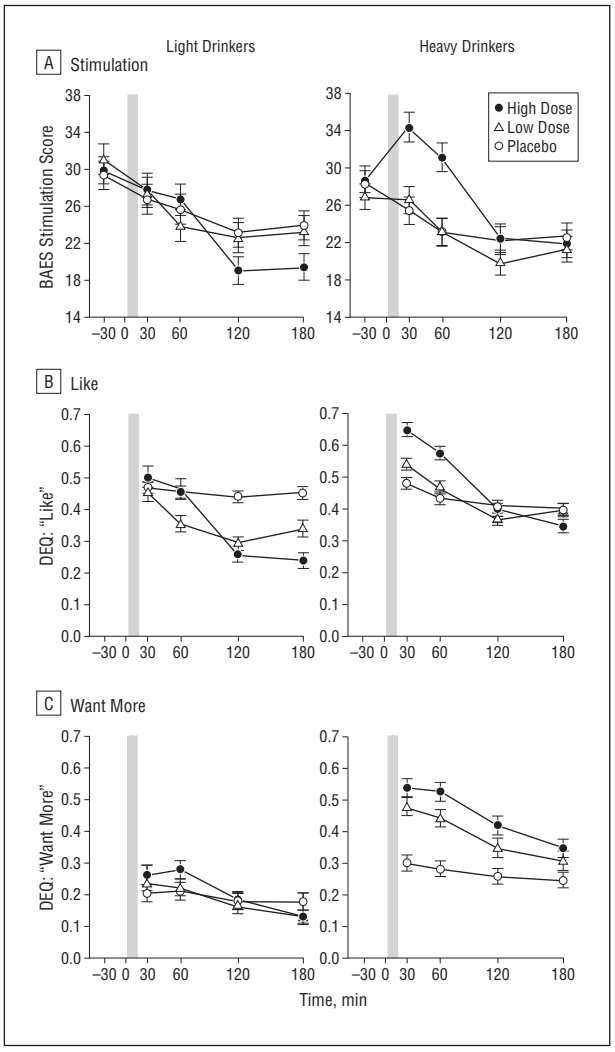


**Figure 2.** Heavy and light drinkers' subjective stimulant and rewarding responses, including the Biphasic Alcohol Effects Scale (BAES; range, 10-70) stimulation (A) and the Drug Effects Questionnaire (DEQ; range, 0.0-1.0) for *like* (B) and *want more* (C) during the sessions. Post hoc analysis of a significant group×dose×time interaction revealed that for *stimulation* at the high dose, heavy drinkers had higher ratings than light drinkers at 30 minutes ($P<.05$) and 60 minutes ($P<.06$). Post hoc analysis of a significant group×dose interaction for *like* at the high dose revealed that heavy drinkers had higher ratings than light drinkers at 30, 60, and 120 minutes ($P<.01$ for all), and a significant group×dose interaction for *want more* at the high dose and low dose revealed that heavy drinkers had higher ratings than light drinkers at all time points ($P<.001$ for all). The shaded bar indicates the alcohol drinking interval from time 0 to 15 minutes. Error bars indicate standard error.

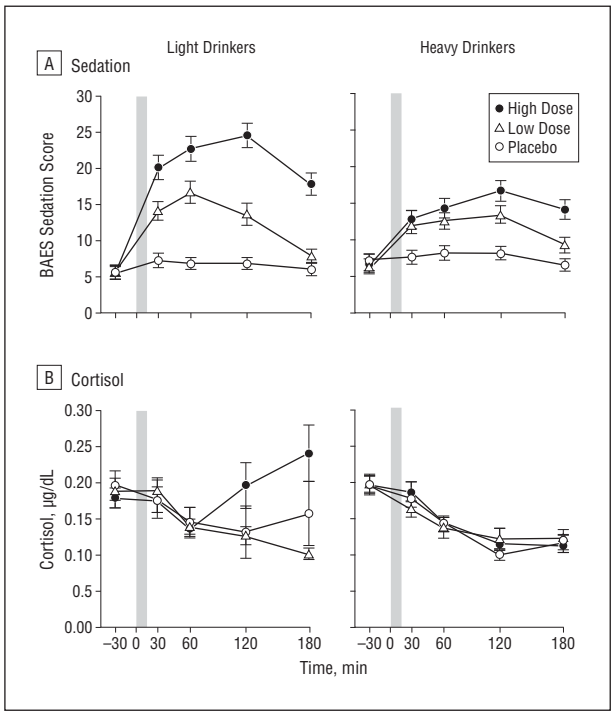


**Figure 3.** Heavy and light drinkers' Biphasic Alcohol Effects Scale (BAES; range, 10-70) sedation (A) and salivary cortisol (B) responses during the sessions. Post hoc analysis of a significant group×dose×time interaction revealed that for *sedation* at the high alcohol dose, light drinkers had higher ratings than heavy drinkers at 30, 60, and 120 minutes ($P<.001$ for all) and at the low dose, light drinkers had higher ratings than heavy drinkers at 60 minutes ($P<.05$). Post hoc analysis of a significant group×dose×time interaction for *cortisol* at the high dose revealed that the light drinkers had higher levels than heavy drinkers at 120 and 180 minutes ($P<.01$ for all). The shaded bar indicates the alcohol drinking interval from time 0 to 15 minutes. Error bars indicate standard error. (To convert cortisol to nanomoles per liter, multiply by 27.588).

Analyses using the generalized estimation equations approach confirmed that in HD, greater alcohol stimulation, greater liking, greater wanting, and lower sedation at the high dose predicted greater binge drinking frequency during follow-up ($P < .001$ for all). Greater liking and wanting responses to the low dose of alcohol also related to future binge drinking, but again these were not as strong as those observed with the high dose. Composite generalized estimation equations models that included all the significant alcohol responses indicated that greater alcohol stimulation ($P<.05$), greater liking ($P<.001$), and lower sedation ($P<.05$) for high dose remained significant predictors of future drinking. These analyses were repeated for alcohol responses during the ascending (30-minute) and descending (120-minute) BrAC limbs. On the ascending limb, alcohol wanting ($P<.001$) was a significant predictor of future drinking, and on the descending limb, liking ($P<.001$), wanting ($P<.01$), and less sedation ($P<.01$) predicted future drinking. Although disinhibited personality and FH predicted future drinking in HD, controlling for these factors did not alter the relationships between alcohol responses and subsequent drinking behavior. For HD, increases in liking (odds ratio [OR] {SE}, 29.81 {29.42}; $P=.001$) and want more (OR [SE], 7.43 [5.32]; $P=.005$) were significantly associated with alcohol use disorder diagnosis during follow-up. When binge drinking pattern was included in the model, the magnitude of association for alcohol response to alcohol use disorder was reduced (like: OR [SE], 14.64 [15.04]; $P<.01$; and want more: OR [SE], 3.51 [2.64]; $P=.10$), suggesting that binge drinking partially (like) or fully (want more) mediated the relationship between alcohol response and subsequent alcohol use disorder.

## COMMENT

We have replicated and extended our group's prior preliminary findings[20,21] demonstrating that HD report greater acute subjective positive effects and lesser sedative and cortisol response to an intoxicating dose of alcohol than do LD. Multivariate models in the HD revealed that both

**Table 2. Bayesian Information Criterion (BIC) and Model Selection**

| No. of Trajectory Groups | Drinkers: Light (n=86) BIC | Light Null Model[a] | Light $2\ln(B_{10})$[b] | Drinkers: Heavy (n=104) BIC | Heavy Null Model[a] | Heavy $2\ln(B_{10})$[b] |
|---|---|---|---|---|---|---|
| 1 | –683 | | | –2729 | | |
| 2 | –661 | 1 | **44** | –2663 | 1 | 132 |
| 3 | –669 | 2 | –17 | –2642 | 2 | 42 |
| 4 | –681 | 3 | –22 | –2632 | 3 | **20** |
| 5 | –697 | 4 | –33 | –2632 | 4 | 0 |
| 6 | –707 | 5 | –20 | –2646 | 5 | –28 |

[a] The number of trajectory groups in the comparison model.
[b] $\ln(B_{10}) \approx 2\Delta BIC$, ie, twice the difference in BIC between the 2 models, was used to determine the best model to describe quarterly frequency of binge drinking. Using $2\ln(B_{10}) \geq 6$ as a strong evidence for rejecting the null model,[80] a 4-trajectory group model in heavy drinkers and a 2-trajectory group model in light drinkers best described the data (indicated in bold).

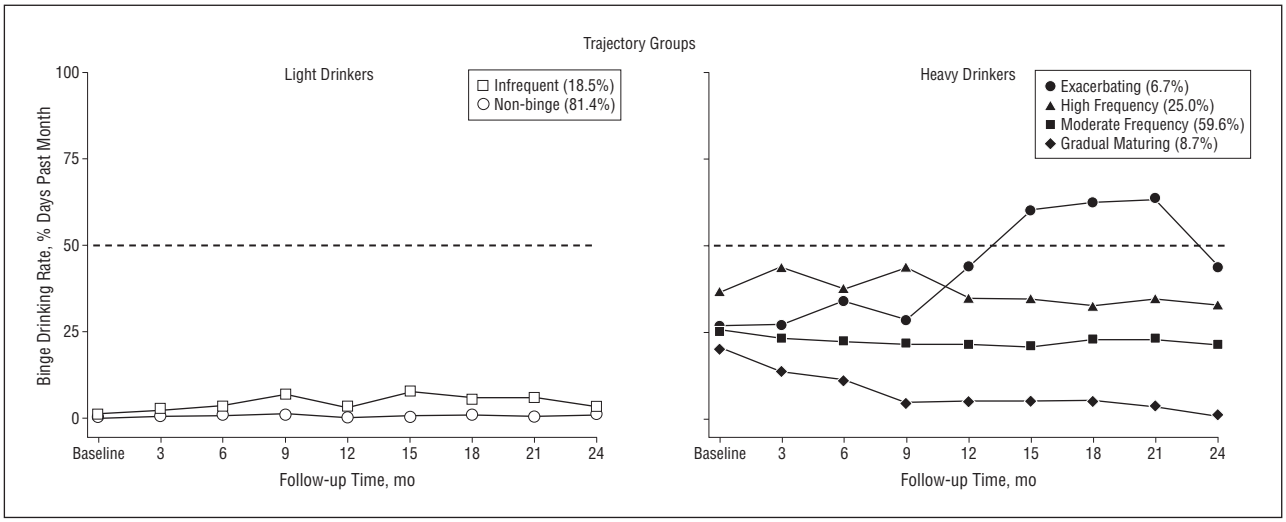


**Figure 4.** Trajectory groups during the 2-year follow-up. Trajectory data were based on the self-reported frequency of past-month binge drinking days obtained at each quarterly interval. A discrete mixture modeling approach determined by the Bayesian Information Criterion for model selection revealed a 2-trajectory group (nonbinge and infrequent binge) model for the light drinkers and a 4-trajectory group (gradual maturing, moderate-frequency binge, high-frequency binge, and exacerbating) model for the heavy drinkers best described the data.

the positive (more stimulation, like, and want more) and negative (less sedation) response factors were significant independent predictors of binge drinking during the subsequent 2 years. These findings were observed even after taking into account other risk factors for problem drinking, such as sex, race, FH, educational level, and disinhibited personality.[2,31] Thus, young adult HD who experience heightened stimulant and rewarding and diminished sedative effects of alcohol are at risk for escalation of binge drinking over time. They also consume more alcohol overall (typical frequency, quantity, and maximum quantity) and experience clinically relevant outcomes, such as greater alcohol consequences and higher rates of *DSM-IV* alcohol use disorders (Table 2).

Although the finding that heavier drinkers enjoy the effects of alcohol more than lighter drinkers seems intuitive, there has been limited evidence thus far to support this notion. Indeed, the prevailing model, the low-level response theory, posits that persons who experience a lower level of response to alcohol will engage in heavier drinking over time because they do not feel the internal cues of intoxication.[88] Our data partially support this theory because HD exhibited reduced subjective sedative and cortisol responses after drinking, compared with the responses of LD, and lack of sedative responses predicted future drinking. However, alcohol markedly increased positive-like effects during ascending to peak BrAC in this group, and these responses also predicted future drinking. In contrast, LD experienced significant increases in sedation during the ascending limb that was sustained for several hours, without concomitant stimulating or rewarding effects. Collectively, these responses may serve as a protective factor underlying these drinkers' ability to "put the brakes on" and limit their drinking. Taken together, the results indicate that the low-level response theory should be revised to include heightened sensitivity to rewarding and stimulating alcohol effects as equally important predictors as lack of sedative responses in the development and maintenance of problematic drinking among at-risk persons. Furthermore, we propose a *modified differentiator model* to focus on stimulant, rewarding, and sedative effects without connec-

**Table 3. Alcohol Use Disorder Diagnoses and Other Drinking Characteristics During the 2-Year Follow-up Among the Trajectory Groups[a]**

| | Light Drinker Trajectory Group | | | Heavy Drinker Trajectory Group | | | | |
|---|---|---|---|---|---|---|---|---|
| *DSM-IV* Diagnoses[b] | Nonbinge (81.4%) | Infrequent Binge (18.6%) | *P* Value | Gradual Maturing (8.7%) | Moderate Frequency (59.6%) | High Frequency (25.0%) | Exacerbating Binge (6.7%) | *P* Value |
| Alcohol abuse | 6 | 25 | <.05 | 0 | 63 | 81 | 86 | <.001 |
| Alcohol dependence | 0 | 0 | NS | 11 | 8 | 31 | 57 | <.001 |
| Alcohol drinking behaviors[c] | | | | | | | | |
| Dr-InC 2R score (total) | 5.16 (0.73) | 7.81 (1.25) | NS | 7.67 (1.98) | 19.44 (1.00) | 24.85 (2.19) | 33.00 (4.23) | <.001 |
| AUDIT score | 3.47 (0.24) | 5.50 (0.53) | <.001 | 4.89 (0.48) | 11.81 (0.42) | 15.50 (0.70) | 21.29 (1.08) | <.001 |
| Average No. of drinking days per month | 5.89 (0.43) | 8.85 (0.84) | <.01 | 7.13 (0.99) | 12.32 (0.49) | 14.33 (0.64) | 19.07 (1.47) | <.001 |
| Average No. of drinks per drinking day | 1.80 (0.08) | 2.58 (0.21) | <.001 | 2.67 (0.25) | 4.91 (0.21) | 5.80 (0.36) | 5.81 (0.53) | <.001 |
| Average No. of binge days per month | 0.19 (0.03) | 1.35 (0.14) | <.001 | 1.76 (0.33) | 6.27 (0.18) | 10.44 (0.25) | 12.79 (0.67) | <.001 |
| Maximum No. of drinks consumed on 1 occasion | 2.69 (0.11) | 4.98 (0.11) | <.001 | 4.81 (0.68) | 9.28 (0.33) | 11.63 (0.69) | 14.25 (1.02) | <.001 |

Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; Dr-InC 2R, Drinker Inventory of Consequences–Recent.

[a] Data are given as mean (SEM) or percentage.

[b] *DSM-IV* diagnoses derived from annual Structured Clinical Interview for *DSM-IV* Axis 1 disorders and coded positive if criteria were met during either 12- or 24-month follow-up.

[c] Dr-InC 2R and AUDIT are average maximum score at 12- or 24-month follow-up; number of alcohol drinking days, number of drinks per drinking day, number of binge days per month, and maximum number of drinks were the average of all 8 quarterly follow-ups. *P* values determined by $\chi^2$ or Fisher exact test for *DSM-IV* diagnoses and by linear trend analysis for alcohol drinking behaviors.

tion to a specific BrAC limb or, conversely, to simplify the model and to focus on effects observed during peak BrAC.

The present study findings are also relevant to the incentive-sensitization theory of addiction.[89-91] This theory posits that sensitization and crucial neuroadaptations within mesolimbic dopamine systems[92,93] may underlie the motivational reward properties (wanting) of a drug, but not the hedonic reward value (liking) of the drug, in persons with substance dependence. However, in this study, we observed that among nondependent HD, both motivational and hedonic aspects of reward were associated with increased frequency of binge drinking over time. Interestingly, in composite prediction models, wanting more alcohol during the ascending and descending limbs of the BrAC curve predicted subsequent binge drinking during follow-up. We may speculate that early in a binge drinking episode, alcohol may elicit heightened desire for alcohol, leading to impaired control and continued drinking. As modeled in this acute administration paradigm, abrupt cessation of drinking results in a sharp decrease in stimulation and liking, with sustained wanting that may underlie desire for further drinking to offset reduction of hedonic effects. Although acute responses to the high alcohol dose producing peak BrACs of 0.08% to 0.09% were more informative than responses to the lower dose, future studies of higher alcohol doses or sustained drinking for a longer interval may help discern whether positive effects decrease (ie, acute tolerance), remain elevated, or increase over time. Such studies would offer an ecologically valid model of more extreme binge episodes. Indeed, among the highly frequent and exacerbating HD binge drinkers, maximal drinking amounts were from 11 to 14 drinks on an occasion (Table 3), resulting in BrACs that would likely be 2 to 3 times the legal limit for driving.

There were several strengths of this study, including the use of a within-subjects, dose-ranging, and placebo-controlled design with intensive follow-up. Responses were obtained at baseline and repeated at several junctures during the course of the BrAC curve, expectancies were minimized by blinding beverage content, and ecological validity was maintained by using a trained research assistant to interact with the participant in a quasi-social context, albeit a paradigm that did not completely mimic all aspects of social drinking. Drinking outcomes were validated by assessment of alcohol consequences and *DSM-IV* diagnoses. Finally, the results were observed within a diverse sample of both men and women of various racial backgrounds, which served to increase generalizability, in contrast to prior studies focusing on white male participants.[8,18,23] This latter issue may be relevant in terms of the lack of systematic FH effects observed for acute subjective and objective alcohol responses, as reported by Brumback et al[67] and Roche and King.[74] Given that participants were enrolled regardless of FH, the subgroup of sons of alcoholic fathers was relatively small, potentially reducing statistical power to detect FH effects. However, positive FH did predict increases in binge drinking over time, and similar to prior research findings, alcohol responses were predictive of future drinking regardless of FH classification.[8] Further research using a priori stratifications of both drinking pattern and FH may provide a more thorough examination of the relationship and possible interactive effects of these risk factors to alcohol response and future drinking behaviors.

The study was limited by the legal requirement that participants be a minimum of 21 years old to be given alcohol, so it is unclear whether the findings can be generalized to even younger drinkers. This is particularly important because the ages of 18 to 20 years represent the highest prevalence of binge drinking and alcohol use dis-

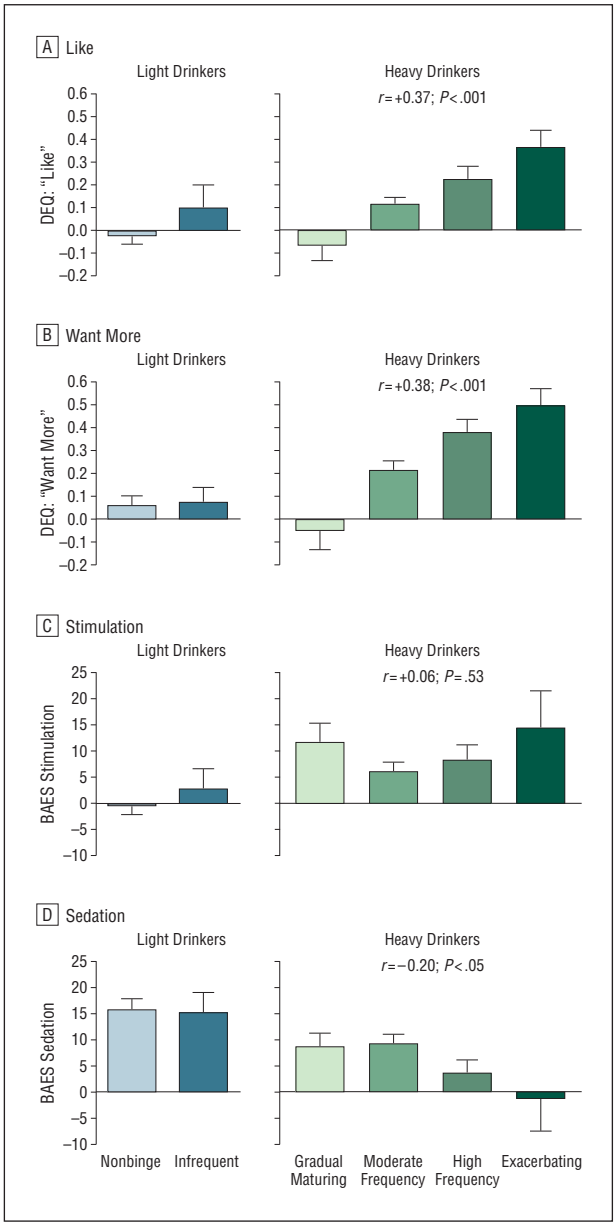


**Figure 5.** Heavy and light drinkers' trajectory groups' initial alcohol responses, including the Drug Effects Questionnaire (DEQ; range, 0.0-1.0) for *like* (A) and *want more* (B) and the Biphasic Alcohol Effects Scale (BAES; range, 10-70) for *stimulation* (C) and *sedation* (D). Alcohol responses are indicated as the mean for each trajectory group based on participants' change score: high dose (60 minutes - baseline) – placebo (60 minutes - baseline). In light drinkers, there were no significant associations of alcohol response to trajectory group. In heavy drinkers, higher ratings for *like* ($P<.001$) and *want more* ($P<.001$) and lower ratings for *sedation* ($P<.05$) were significantly linearly associated with drinking trajectory group. Error bars indicate standard error.

orders.[36] Second, participants' average age was 25 years, which for many HD corresponds to 5 to 7 years of regular binge drinking. Therefore, it was not possible to determine whether alcohol-induced responses were constitutional or acquired with repeated exposure to alcohol. This question may be best addressed using animal models. Finally, although the quarterly follow-up assessments after the laboratory sessions were sufficiently frequent to show fluctuations in drinking for 2 years, the length of this interval may not have been adequate for the full range of drinking and related alcohol use disorders to emerge. To address this issue, we plan to continue to follow up these participants to examine their drinking patterns over a longer time.

In summary, we propose revisions to current theories of the role of alcohol response to subsequent drinking problems in at-risk individuals, and we set forth a modified differentiator model to focus on both positive (stimulant, as well as hedonic and motivational rewarding) and sedative alcohol effects either without ties to a specific BrAC limb, or simply at peak BrAC. Heavy drinkers experience markedly different responses to alcohol than do LD. For LD, an intoxicating dose of alcohol produces tired and sluggish feelings and activates release of the stress hormone cortisol. During a 2-year interval, few of them increased their drinking. In contrast, HD showed a variety of drinking trajectories during the 2 years of follow-up, and those experiencing less positive and more sedative acute alcohol effects gradually matured out of binge drinking over time. On the other hand, HD with heightened rewarding effects of alcohol perpetuated and increased binge drinking frequency over time, thereby increasing the likelihood of meeting *DSM-IV* diagnoses of alcohol abuse and dependence.

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