Archival Report

A Prospective 5-Year Re-examination of Alcohol Response in Heavy Drinkers Progressing in Alcohol Use Disorder

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ABSTRACT

BACKGROUND: The main neurobiological theories of the development of addiction, including tolerance, sensitization, incentive-sensitization, and allostasis, have not been tested in longitudinal human alcohol response research. To address this issue, we conducted the first controlled prospective investigation of subjective and neuroendocrine responses to alcohol measured over a 5-year interval in at-risk young adult heavy drinkers (HD) and light drinker control subjects.

METHODS: Participants were 156 individuals, 86 heavy drinkers and 70 light drinkers, undergoing an initial oral alcohol challenge testing (.8 g/kg alcohol vs. placebo) and an identical re-examination testing 5 to 6 years later. Alcohol use disorder (AUD) symptoms and drinking behaviors were assessed in the interim follow-up period.

RESULTS: At re-examination, HD continued to exhibit higher sensitivity on alcohol's stimulating and rewarding effects with lower sensitivity to sedative effects and cortisol reactivity, relative to light drinkers. In HD with high AUD symptom trajectories over follow-up, heightened alcohol stimulation and reward persisted at re-examination. HD with low AUD symptoms showed reduced alcohol stimulation over time and lower reward throughout compared with the HD with high and intermediate AUD symptoms.

CONCLUSIONS: Results support the early stage phase of the allostasis model, with persistently heightened reward sensitivity and stimulation in heavy drinkers exhibiting AUD progression in early mid-adulthood. While there are multiple pathways to development of a disorder as complex as AUD, maintenance of alcohol stimulatory and rewarding effects may play an important role in the continuation and progression of alcohol addiction.

Keywords: Alcohol response, Heavy drinking progressing with AUD, Reward sensitivity, Stimulation, Subjective, Tolerance

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Alcohol use disorder (AUD) is associated with numerous consequences for the individual and society, including psychological, occupational, and health consequences, as well as public safety harms and annual financial costs exceeding $223 billion in the United States (1). Thus, identifying the mechanisms underlying the development and maintenance of AUD has become increasingly important for AUD prevention and treatment. Four leading neurobiological theories of the development of addiction include tolerance, sensitization, incentive-sensitization, and allostasis. These theories purport nervous system adaptations to repeated alcohol exposure underlie the progression of compulsive drinking and development of addiction, but they lead to differential predictions about the nature of these responses over time. While these theories are crucial to our understanding of AUD, they are largely based on animal data and their predictions have not yet been directly tested in controlled longitudinal human studies. The present study provided the first comprehensive repeated evaluation of alcohol responses in at-risk drinkers to test these neurobiological theories of AUD progression.

The most longstanding theory of alcohol adaptation is chronic tolerance (2–7), i.e., the need for markedly increased amounts of alcohol to achieve a desired effect or experiencing markedly diminished effects with continued use of the same amount of alcohol. Tolerance, a diagnostic criteria for AUD from DSM-III (1980) to DSM-5 (2013) (8), implies that attenuation of subjective alcohol responses over time plays a key role in the development of addiction. In contrast, the sensitization theory asserts that greater stimulant effects over time underlie addictive processes (9), based on rodent data showing that stimulant-like and locomotor alcohol responses increase after repeated exposures (10,11). These effects are particularly strong in selectively bred mouse lines (12–14); sensitized responses may also include adrenal hormones (15). The incentive-sensitization theory of addiction (16,17) also emphasizes the sensitization process but specifies that repeated use of a drug produces neuroadaptations that sensitize motivational reward to drugs and associated drug stimuli (i.e., processes of wanting) distinct from the neurocircuitry mediating hedonic reward (liking), which may not

sensitize over time. Finally, allostatic theory asserts heightened brain reward sensitivity and positive reinforcement characterize the early stages of addiction (18), but reward insensitivity and negative reinforcement underlie the later and more severe stages (18–20). Thus, while some researchers may not agree on the contributions of positive versus negative reinforcement factors underlying addiction (21,22), there is consensus on the critical need for longitudinal controlled human alcohol response investigation. Human studies in this area have been limited to retrospective patient reports (23), postmortem brain tissue methods (24), or cross-sectional laboratory paradigms (2,3,25–29), none of which directly measure alcohol responses in the same individuals over time. The few published test-retest studies of alcohol responses have included only brief between-session intervals with a focus on measurement reliability (30,31).

To address this issue, we conducted the Chicago Social Drinking Project (CSDP), a prospective alcohol response re-examination study. The CSDP examined 190 nonalcohol dependent young adult heavy (HD) and light drinkers (LD) who were primarily in their 20s (mean age 25.6 ± 3.2 SD years) at enrollment. Our previously published results showed that compared with light drinkers, heavy drinkers exhibited higher alcohol sensitivity, in terms of subjective stimulation and reward (liking and wanting) (29), as well as lower sensitivity, in terms of subjective sedation (29) and salivary cortisol reactivity (29,32). These findings were replicated in a second independent heavy drinker cohort using identical procedures (33). Further, in heavy drinkers, greater alcohol stimulation and reward and lower sedation predicted binge drinking escalations at 2-year follow-up (29), with greater stimulation and reward predicting more AUD symptoms experienced through 6 years (34).

In the current phase of CSDP, participants were invited back between their fifth and sixth year of the study to participate in two re-examination laboratory sessions. The goal was to conduct empirical tests of the neurobiological theories of alcohol adaptations underlying the propensity to develop addiction. We examined whether the alcohol response differences observed at initial testing persisted or changed in heavy versus light drinkers and whether the degree of change related to trajectories of AUD progression among the heavy drinkers. Tolerance theory would be supported if the heaviest drinkers over time showed an overall reduced alcohol response at re-examination compared with initial testing, whereas sensitization would be supported if the heaviest drinkers showed higher stimulant responses. The allostasis model's early phase of addiction, which may most closely match a 5-year interval in young adults, would be supported if alcohol reward sensitivity was maintained, and the later stage would be supported if reward sensitivity was diminished. Finally, increases over time in alcohol wanting would support the incentive-sensitization theory.

METHODS AND MATERIALS

Design

The CSDP is a within-subject, double-blind, randomized-order study of responses to alcohol and placebo beverages in 190 young adult nonalcohol dependent drinkers. The study was approved by the University of Chicago Institutional Review Board. Initial laboratory testing was conducted March 2004 to July 2006, and re-examination testing was conducted March 2009 to October 2011. Participants returned for re-examination, on average, 63 months (±1.5 SD) after their initial assessment. Both testing phases included two 4½-hour individual sessions separated by at least 24 hours and were conducted at the Clinical Addictions Research Laboratory at the University of Chicago. Participants completed measures before and after ingesting a blinded beverage that contained either .8 g/kg alcohol or placebo administered in random order at each phase.

Initial Testing Phase

Participants were recruited via local media and internet advertisements and word-of-mouth referrals. Initial inclusion criteria were age 21 to 35 years; weight 110 to 210 pounds; good general health; not pregnant or lactating; no current or past major medical or Axis I psychiatric disorders, including alcohol and substance dependence (other than nicotine); and no current use of any centrally acting medications. The medical screening by the study nurse included a brief physical assessment, health history, vital signs, a blood draw to confirm normal liver enzyme levels (≤ 2 SD of normal range), a urine toxicology screen (cocaine, opiates, benzodiazepines, amphetamines, barbiturates, and phencyclidine), and pregnancy test for women. A trained research assistant conducted the alcohol Quantity-Frequency Interview (35) and the alcohol disorders module from the Structured Clinical Interview for DSM-IV, nonpatient version (36). The participant also completed demographic measures, a two-generational biological family history (FH) tree for alcohol use disorders and the FH Research Diagnostic Criteria for drinking consequences (37), an Alcohol Timeline Followback for past month drinking (38), the Alcohol Use Disorders Identification Test (39), and the Drinker Inventory of Consequences (40). Heavy drinkers were defined as weekly binge drinkers (consuming ≥5 drinks for men and ≥4 drinks for women, per occasion, one to four times weekly) with at least 10 but no more than 40 drinks consumed per week for at least the past 2 years. Light drinkers averaged consuming one to five drinks per week with no/rare binge episodes (≤ 5 times per year). These criteria were based upon established guidelines (41–43) and were consistent with prior studies (44–50). Positive FH was defined as having at least one biological first-degree relative or two or more second-degree relatives with alcohol use disorders.

Laboratory Procedures

The testing sessions for both phases were conducted in the afternoon and commenced between 12:00 PM and 5:00 PM. To reduce alcohol expectancy, the Alternative Substance Paradigm (51) was used. Participants were informed that their allocated beverage might contain a stimulant, sedative, alcohol, or a placebo or a combination of these substances. Upon arrival, the participant completed self-report measures and engaged in objective breath tests to confirm compliance with recent alcohol abstinence. Urine samples were collected before one session, chosen randomly, for toxicology in all

participants and before each session for women to verify nonpregnancy. Participants were interviewed to confirm compliance with 3-hour abstinence from food, caffeine, and smoking. Each participant then consumed a standard snack at 20% of daily kilocalorie needs per body weight (55% carbohydrates, 10% protein, and 35% fat) (52) followed by acquisition of baseline measures for approximately 15 to 20 minutes.

Starting at experimental time 0, the participant consumed his/her beverages presented in lidded, clear plastic cups in two equal portions, with each portion consumed over 5 minutes separated by a 5-minute rest with the research assistant present (45,46,53). The average total beverage volume was 471 mL containing 190-proof ethanol (1% volume for placebo as a taste mask, 16% volume for alcohol beverage). The beverage was prepared with water, a flavored drinking mix, and a sucralose-based sugar substitute. Doses for women were 85% of those for men to adjust for sex differences in total body water (54,55). Dependent measures and breathalyzer tests (Alco-Sensor IV, Intoximeter, St. Louis, Missouri) were repeated at 30, 60, 120, and 180 minutes. Other objective responses were obtained after the subjective measures and these results are presented elsewhere (53,56). Breathalyzer readings were programmed to read .000 mg/dL, with actual values downloaded later. At the end of each session, after breath alcohol concentration (BrAC) was ≤40 mg/dL (57), the participant was transported to his/her lodging using a car service.

Alcohol Responses

The Biphasic Alcohol Effects Scale (58) was used to assess subjective stimulation and sedation, and the Drug Effects Questionnaire (DEQ) (59), using 10 cm visual analog scales, to assess hedonic reward, liking: "Do you LIKE the effects you are feeling now?" (midpoint as neutral) and motivational reward, wanting more: "Would you like MORE of what you consumed, right now?" The instructions asked for current mood state at each time point and did not reveal that alcohol was ingested (60). Saliva samples were provided by participants at each time point via a cotton Salivette (Sarstedt AG & Company, Nümbrecht, Germany). Samples were stored at −20°C and later assayed for levels of the stress hormone cortisol by high sensitivity enzyme immunoassay at the University of Chicago Clinical Resource Center Core Laboratory. The interassay and intra-assay coefficients of variation at initial testing were 6.88% and 7.12%, respectively, and at re-examination were 6.60% and 7.99%, respectively. The main dependent analytic variables were: 1) stimulation and sedation: net change scores from the Biphasic Alcohol Effects Scale, calculated by subtracting the prebeverage rating from the 60-minute postbeverage rating (peak BrAC) in the alcohol session minus the same change score from the placebo session; 2) liking and wanting more: change scores for the DEQ calculated by subtracting the 60-minute postbeverage rating in the alcohol session minus the placebo session, since the DEQ pertains to drug effects and so does not include a prebeverage administration; and 3) cortisol: net change scores calculated by subtracting the prebeverage from the last (180 minutes) postbeverage level minus the same change score

from the placebo session. This later time point was used given the delay in time course for cortisol secretion (29,45,61).

Interim Follow-up Phase

In the interval between initial testing and re-examination, participants completed annual telephone and secured internet follow-ups through 6 years (34), excluding year 3 to avoid participant burden. The follow-ups included similar measures as those at baseline screening, including the Structured Clinical Interview for DSM-IV AUD module (36), TLFB (38), Quantity-Frequency Interview (35), Alcohol Use Disorders Identification Test (39), and Drinker Inventory of Consequences (40). The number of AUD criteria endorsed was the main dependent outcome variable assessed during follow-up to reflect the dimensional nature of these symptoms (62). The DSM-IV criteria were similar to those in DSM-5 (8,62) with the former including an item for alcohol-related legal problems that has since been dropped and excluding the DSM-5 item for craving that had not yet been developed.

At the 5-year follow-up, 186 (97.9%) of the 190 individuals continued to participate, and telephone re-screening was conducted to determine eligibility for re-examination. Of the individuals who continued to participate, 95.7% (178/186) remained eligible: they were current drinkers with no major medical or psychiatric contraindications. From this eligible subject pool of 178 individuals, 156 (87.6%) (82.1% of the original sample, 156/190) returned to participate in re-examination sessions. Participants undergoing re-examination did not differ from those who did not undergo re-examination on major background characteristics or geographic location (all *p*s ≥ .23). As needed, transportation (airfare, local transport, etc.) and lodging arrangements were provided by the study. Figure S1 in Supplement 1 shows the Consolidated Standards of Reporting Trials diagram.

Trajectory Subgroups in HD

Our prior report [King *et al.* (34)] indicated that the HD and LD continued to differ significantly through follow-up on all measures of alcohol drinking behaviors and problems. Table 1 depicts demographic, health, and drinking comparisons between the groups, and Table S1 in Supplement 1 depicts baseline characteristics of the groups. In brief, the LD largely continued with low-risk drinking. While they consumed alcohol more frequently over time, binge drinking and alcohol problems were rare, and they formed one low-risk trajectory group (34). In contrast, the HD comprised three AUD subgroups over time, derived by trajectory analysis that differentiated those with low, intermediate, and high symptoms (Table 1).

Statistical Analysis

Demographic and drinking characteristics were compared across groups for each phase by generalized estimating equations (GEE) (63). Pearson correlations were used to examine the association of each alcohol response (net change in stimulation, sedation, and cortisol; change in like and want more) at initial and re-examination phases. These variables were examined in GEE models testing effects of group (HD,

Table 1. Characteristics of Participants at Retesting and Over Follow-up

Demographics and Health	LD and HD Groups		HD AUD Subgroups		
	LD, $n = 70$	HD, $n = 86$	Low, $n = 26$	Intermediate, $n = 51$	High, $n = 9$
Age (Years)	31.3 (.4)	30.3 (.3)	31.0 (.6)	30.0 (.4)	29.9 (1.2)
Education (Years)	18.0 (.4)	16.2 (.2)[***]	15.9 (.4)	16.3 (.3)	16.0 (1.2)
Sex (Male)	49%	57%	50%	61%	56%
Race (Caucasian)	67%	83%[*]	77%	84%	89%
Family History Positive (AUD)[a]	34%	44%	35%	51%	67%
Age at First Drink (Years)	17.7 (.3)	15.0 (.3)[***]	15.5 (.4)	14.8 (.3)	14.2 (.8)
Beck Depression Inventory	3.1 (.4)	4.3 (.5)	2.3 (.6)	4.7 (.6)	7.8 (1.7)[**,b]
Spielberger State Anxiety (T-Score)	47.7 (.9)	48.8 (.8)	45.9 (1.2)	49.0 (1.1)	56.4 (2.2)[***,c]
Marijuana Use (Weekly or More)	1%	26%[***]	19%	24%	56%[*,d]
Cigarette Use (Weekly or More)	1%	37%[***]	19%	28%	78%[*,c]
Stimulant Use (Monthly or More)[e]	0%	5%	4%	2%	22%[*,c]
Major Axis I Disorder[f]	6%	12%	4%	12%	33%[*,d]
Substance Dependence[g]	0%	11%[*]	0%	12%	33%[*,d]
Nicotine Dependence[f]	0%	19%[***]	8%	22%	56%[*,c]
AST (Units/L)[h]	20.8 (.7)	22.2 (1.2)	23.7 (3.6)	21.3 (.9)	23.1 (2.9)
ALT (Units/L)[h]	20.1 (1.8)	21.6 (2.0)	24.0 (5.8)	20.2 (1.4)	22.1 (4.9)
Average Drinking Over Follow-up[i]					
Frequency (days/month)	6.8 (.5)	12.1 (.5)[***]	10.1 (1.0)	12.5 (.6)	15.5 (2.4)[*,d]
Quantity (drinks/drinking day)	1.8 (.1)	5.0 (.2)[***]	4.0 (.3)	5.1 (.3)	7.5 (.8)[***,b]
Maxima Drinking Over Follow-up[j]					
Maximum # drinks in one occasion	4.6 (.2)	12.6 (.6)[***]	10.7 (1.0)	13.0 (.6)	18.6 (3.0)[***,c]
Binge frequency (days/month)[k]	1.1 (.2)	10.2 (.5)[***]	7.5 (.7)	10.3 (.5)	17.2 (2.5)[***,b]
AUD symptom count	.6 (.1)	2.8 (.2)[***]	0.9 (.2)	3.2 (.2)	6.4 (.6)[***,b]
AUDIT total score	5.3 (.3)	14.8 (.7)[***]	10.2 (.7)	15.6 (.8)	23.8 (1.9)[***,b]
DrInC total score	7.2 (.9)	23.9 (1.4)[***]	14.8 (1.8)	25.0 (1.5)	44.0 (2.6)[***,b]

Values are presented as mean (SEM) or %. Data include measures obtained at the re-examination or a self-report summary of use patterns and symptoms for the year prior to re-examination, unless otherwise noted.

ALT, alanine aminostranferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; DrInC, Drinker Inventory of Consequences (past three months); HD, heavy drinkers; LD, light drinkers; TLFB, timeline followback.

[a]Family history positive defined as having one biological primary or three or more biological secondary relatives with an alcohol use disorder.

[b]High > Intermediate > Low.

[c]High > Intermediate = Low.

[d]High > Low, High = Intermediate.

[e]Stimulant use included both prescription and recreational drugs.

[f]Ever meeting DSM-IV major Axis I diagnosis (depression, anxiety disorders, etc.) or nicotine dependence at any point during the follow-up period.

[g]Seven of the nine substance dependent persons met criteria for cannabinoids, one for cocaine, and one for prescription opiates.

[h]Aspartate aminotransferase and alanine aminotransferase blood tests for liver functioning.

[i]Drink based on standard definition of one drink = 12 oz. beer, 5 oz. wine, or 1.5 oz. liquor, from average of past month TLFB interviews at 1, 2, 4, 5, and 6 years.

[j]Refer to maxima of TLFB or survey measures from 1-, 2-, 4-, 5-, and 6-year follow-up.

[k]Binge defined as ≥5 drinks per occasion for male subjects and ≥4 drinks for female subjects.

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

LD), phase, and their interactions. To further investigate the source of group differences, GEE analyses compared alcohol responses by phase among the three HD AUD trajectory subgroups. If the interaction was not significant, then this term was removed to examine the main effect of group or phase. Since FH is as a potential risk factor for development of alcohol problems (64), analyses were repeated including FH as a covariate with FH coded by two dummy variables: FH positive versus negative, and FH not sure versus negative.

RESULTS

BrAC Comparisons by Test Phase

Figure 1 shows the BrAC curves at initial and re-examination testing for light and heavy drinkers. BrAC peak levels at 60 minutes were slightly higher at initial testing in the HD versus LD (94 vs. 85 mg/dL, respectively, $p < .001$), but at re-examination, there were no differences (89 vs. 85 mg/dL,
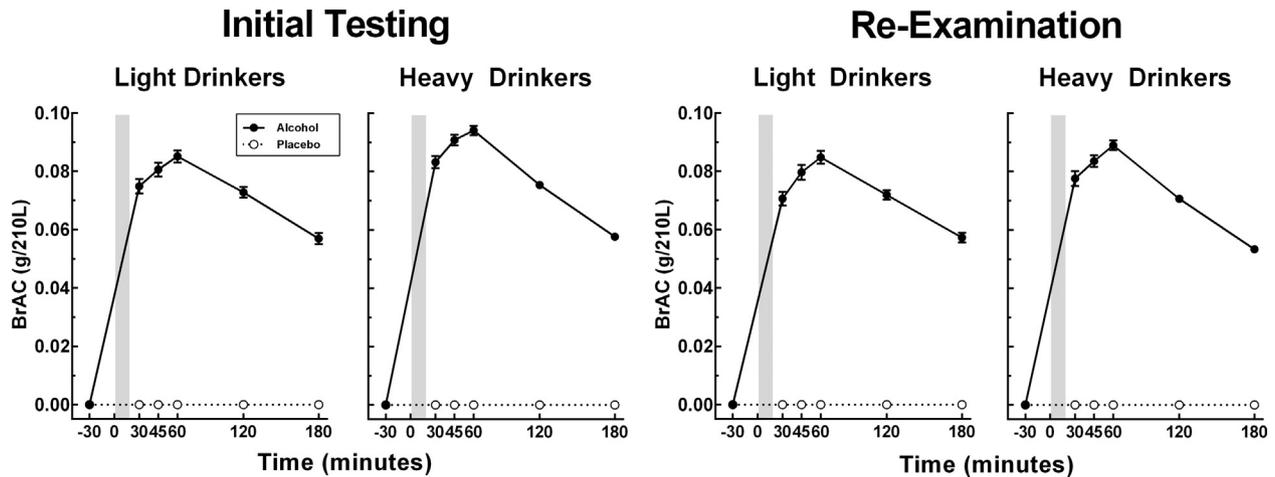
Figure 1. Breath alcohol concentration (BrAC) curve data as mean (SEM) for light and heavy drinkers at initial and re-examination testing.

$p = .126$). All analyses controlled for peak BrAC levels at each testing phase.

Association of Alcohol Responses Over Time

Within-subject associations of each alcohol response between initial and re-examination phases were positive and significant (stimulation [$r = .30$, $p < .001$], liking [$r = .26$, $p < .001$], wanting [$r = .30$, $p < .001$], sedation [$r = .42$, $p < .0001$], and cortisol [$r = .18$, $p < .05$]).

Group Comparisons of Alcohol Responses

Detailed GEE results of the alcohol response analyses for HD and LD and among the three AUD subgroups within HD are summarized in Table 2. In brief, at both phases, relative to LD, HD exhibited higher sensitivity to alcohol stimulating and rewarding effects (Figure 2A–C). HD also had lower sensitivity to sedation (Figure 3A) and cortisol response versus LD (Figure 3B). For the HD subgroups, there was a subgroup × phase interaction for stimulation such that the high AUD subgroup persisted with heightened stimulation at re-examination and the intermediate group persisted at inter-mediate levels, but the low AUD subgroup showed a reduction in stimulation over time. For alcohol reward, there were main effects of AUD subgroup: relative to the low AUD subgroup, the high and intermediate AUD subgroups had persistently higher alcohol liking and wanting over time than the low AUD subgroup. The relationships of stimulation, liking, and wanting were positive for the high and intermediate AUD subgroups, suggesting that stimulation is pleasurable; these correlations were not significant in the low AUD subgroup (Supplemental Results in Supplement 1). The AUD subgroups did not differ on alcohol sedation or cortisol response (Figure 3A, B). All findings remained after including age, sex, race, and FH, as well as psychiatric disorders and substance and nicotine dependence as covariates in the same models.

Finally, analyses were repeated for stimulating and reward-ing alcohol responses at rising and declining BrAC limbs, i.e., 30- and 120-minute net change scores, for each phase (Figure S2 and Tables S2 and S3 in Supplement 1). Results showed that the magnitude of responses and the differences between

LD and HD and across AUD subgroups were largely similar during the rising limb as they were during peak BrAC at 60 minutes. At the declining limb, stimulating and rewarding responses were lower in magnitude than at the earlier time points, but heightened responses remained in HD, particularly for wanting in the high AUD subgroup.

DISCUSSION

This study was the first longitudinal examination of alcohol responses measured under controlled conditions in heavy binge drinkers varying in their progression of AUD from early through mid-adulthood. In this phase of the CSDP, we report that the heightened alcohol stimulation and reward and lower sedation and cortisol responses observed in heavy versus light drinkers at initial testing (29) remained at re-examination testing 5 to 6 years later. Specifically, among heavy drinkers with increasing symptoms of AUD, at re-examination at a peak BrAC near 90 mg/dL, heightened stimulating and rewarding alcohol effects with lower sedative and neuroendocrine effects persisted. In contrast, heavy drinkers with few emerging symptoms of AUD (and markedly less binge drinking) showed reduced alcohol stimulation at re-examination with persistent lower alcohol reward than in heavy drinkers with either intermediate or high AUD symptoms. Light drinkers largely continued low-risk drinking and rare AUD symptoms over time with an overall protective alcohol response footprint: persis-tently low sensitivity to alcohol stimulation and reward and high sensitivity to alcohol sedative and stress hormone effects. All these aforementioned effects remained after controlling for covariates and other risk factors, such as FH, and group differences were largely apparent on the rising and declining limbs of the BrAC, as well as at peak BrAC.

In terms of the neurobiological theories of the development of addiction through alcohol response adaptation, the findings in those progressing with alcohol problems provide initial support for the early stage of addiction in the allostasis model with heightened stimulation and reward sensitivity that did not diminish over time. Koob and Le Moal (65) coined the later stage of addiction as the dark side of addiction because it is characterized by development of reward insensitivity and

Table 2. GEE Analysis Summary of Alcohol Responses in Light and Heavy Drinkers by Testing Phase and HD AUD Subgroups by Testing Phase

Alcohol Responses	Group (LD vs. HD)			Phase			Group × Phase			Postestimation Comparisons[a]
	β	SE	p	β	SE	p	β	SE	p	
Stimulation	6.19	2.54	.015	1.41	2.15	.512	−1.67	2.92	.567	HD > LD
Like	10.86	4.69	.021	−5.37	4.29	.211	2.76	5.80	.634	HD > LD
Want More	13.82	5.80	.017	−4.86	5.17	.348	11.09	7.00	.113	HD > LD
Sedation	−7.86	2.63	.003	−3.63	2.11	.086	1.28	2.86	.655	HD < LD
Cortisol	−.15	.05	.004	−.03	.05	.579	.05	.06	.467	HD < LD

Alcohol Responses	HD AUD Subgroup			Phase			AUD Subgroup × Phase			Postestimation Comparisons
	β	SE	p	β	SE	p	β	SE	p	
Stimulation	1.10	2.49	.659	−11.65	5.39	.031	6.20	2.84	.029	Low AUD: Initial > Re-Exam Phase[b]
Like	16.59	4.45	<.001	−2.48	10.27	.809	−.80	5.40	.883	High > Intermediate > Low[c]
Want More	12.60	4.89	.010[d]	6.34	4.48	.157	3.46	7.24	.633	High = Intermediate > Low[c]
Sedation	4.28	2.77	.123[e]	5.23	5.72	.360	−4.35	3.01	.148	N/A
Cortisol	.02	.03	.342[e]	.005	.07	.940	.06	.03	.854	N/A

Results from GEE analyses [coefficient (β), standard error (SE), and p value] for alcohol response measures for group (HD vs. LD) or AUD subgroup (the HD AUD subgroups), phase (initial, re-examination), and their interaction(s). Alcohol responses were either net change (stimulation, sedation, and cortisol) or change (like, want more) scores from placebo for each phase.

AUD, alcohol use disorder; GEE, generalized estimating equation; HD, heavy drinkers; LD, light drinkers; N/A, not applicable.

[a]Group (HD vs. LD) comparisons.

[b]Group × phase comparison.

[c]Subgroup (High, Intermediate, Low AUD) comparisons.

[d]The main subgroup effect was significant after the interaction term was removed.

[e]The main effects remained insignificant in the model when the interaction terms were removed.

drinking behaviors related to negative reinforcement. This type of alcohol adaptation was not observed in heavy drinkers progressing with AUD, with the majority of persons in this subgroup either maintaining or increasing heightened stimulation at re-examination, with only 2 of 9 high AUD individuals showing a lessening of response. This could be due to several reasons: a 5-year re-examination interval in humans may not be sufficiently long to show later-stage changes in reward sensitivity; allostasis may only occur in the most extreme alcoholics with significant withdrawal not selected for the sample due to ethical constraints; or the allostasis phenomena modeled in animal studies may not translate to the development of human AUD.

Importantly, there was little support for tolerance in terms of a comprehensive subjective phenomenon (8) in the progression of AUD, as "markedly diminished effects at the same amount of alcohol" were not evident in heavy drinkers as a group or in the subgroup showing the high AUD trajectory over time. Rather, initially heavy drinkers with fewer AUD symptoms over time showed tolerance in alcohol stimulation at retesting. Whether this change was the cause or result of their less intensive bingeing over time or an associated feature unrelated to their drinking course remains to be determined. Nonetheless, if tolerance were the key mechanism in the progression of AUD, reduced levels of stimulation in those with greater AUD symptoms in the interim would have been observed.

Finally, the results did not support sensitization theory, as heavy drinkers with progressive AUD subjects maintained but did not further increase their already heightened sensitivity to stimulation. Motivational reward (wanting) was persistently elevated in heavy drinkers with both intermediate and high AUD symptoms. Thus, incentive sensitization, i.e., an increase in alcohol's incentive salience (wanting), was not evident over the interval tested, and hedonic reward (liking) also remained elevated in heavy drinkers with high AUD. Putting these data together, it is possible that neither tolerance nor sensitization processes were observed because they may have taken place earlier in the drinking history of these young adults or responses approached ceiling or floor effects for what can be observed in the controlled laboratory environment. It is also possible that behavioral and objective biomarkers in animal models (locomotion, tail flick, conditioned incentive procedures, etc.) do not directly translate to subjective responses and the progression of human AUD. While objective biomarkers in animal models are well developed, human subjective responses and clinical phenomena are crucial to our understanding of the processes affecting addiction propensity.

The findings inform our conceptualization of alcohol responses during the processes of continued excessive and harmful drinking leading to AUD. Previous studies relying on proxy measures of brain-behavior relationships to alcohol response (2,3,23–29) have not been able to address within-person changes or stabilization in alcohol response over time. The current study's focus on evaluating alcohol responses longitudinally, in combination with new developments in molecular and cellular studies of the basis of addiction (66), may help identify important substrates for addictive processes leading to and sustaining alcohol use disorder. The findings may have relevance to medication development, as altering euphoric and pleasurable effects of alcohol would be important targets for novel treatments and are hypothesized to underlie in part the efficacy of opioid receptor antagonists,
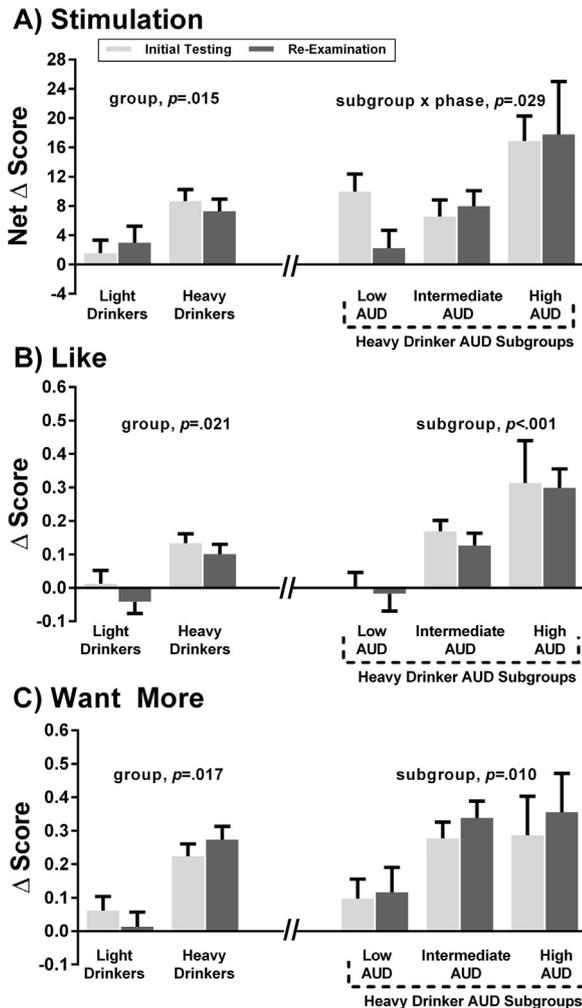
A) Stimulation

B) Like

C) Want More

Figure 2. **(A–C)** Alcohol stimulation, liking, and wanting at initial and re-examination phases. Data are shown for light (*n* = 70) and heavy drinker (*n* = 86) groups, as well as the heavy drinker alcohol use disorder (AUD) trajectory subgroups, including low AUD (*n* = 26), intermediate AUD (*n* = 51), and high AUD (*n* = 9). **(A)** The net change score (alcohol session peak breath alcohol concentration minus baseline change score minus the same change score for the placebo session) for the Biphasic Alcohol Effects Scale stimulation; three outliers (<3 SD below mean) were removed in this analysis. **(B, C)** The Drug Effects Questionnaire like and want more change scores (alcohol session minus placebo session), respectively. Generalized estimating equation results are depicted for group and group × phase effects; see Table 2 for postestimation testing results.

A) Sedation

B) Cortisol

Figure 3. **(A, B)** Alcohol sedation and cortisol response at initial and re-examination phases. Data are shown for light (*n* = 70) and heavy drinker (*n* = 86) groups, as well as the heavy drinker alcohol use disorder (AUD) trajectory subgroups, including low AUD (*n* = 26), intermediate AUD (*n* = 51), and high AUD (*n* = 9). **(A)** The net change score (alcohol session peak breath alcohol concentration minus baseline change score minus the same change score for the placebo session) for the Biphasic Alcohol Effects Scale sedation. **(B)** The net change score (alcohol session 180 minutes minus baseline change score minus the same change score for the placebo session) for salivary cortisol levels; three outliers (two >3 SD above mean, one <3 SD below mean) were removed in this analysis. Generalized estimating equation results are depicted for group effects.

including naltrexone and nalmefene (67–76). Moreover, innovative early intervention and psychoeducation efforts (77,78) may be further refined to target information on higher sensitivity to stimulating and rewarding alcohol effects to prevent longer-term hazardous dependent drinking.

Study strengths included a placebo-controlled prospective design with 624 individual laboratory sessions with alcohol and placebo conditions, excellent follow-up retention, and inclusion of a comparison low-risk group to account for general drift and temporal effects. Limitations included that the re-examination interval may not have been sufficient to observe the extent of neuroadaptive responses to alcohol
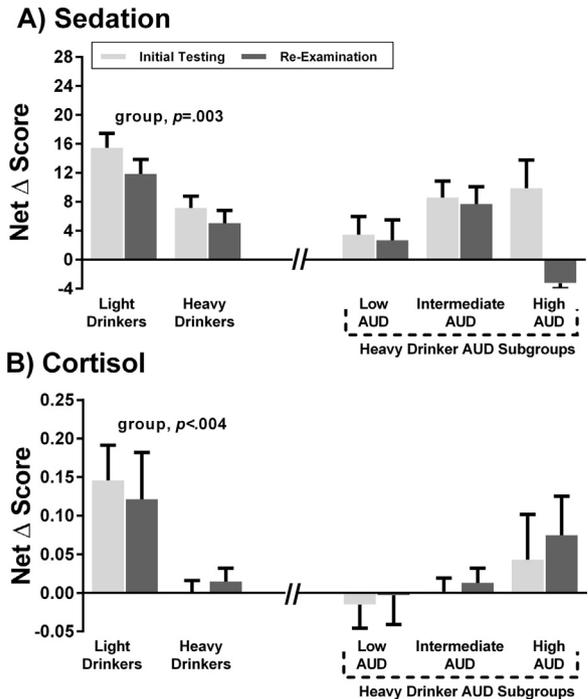
(18), and beverages were consumed over short intervals to capture direct alcohol effects and minimize variability, but this may not translate to typical drinking situations. Further, trajectory analyses resulted in unequal subgroup sample sizes and participants under age 21 were not enrolled due to legal restrictions of alcohol administration in the United States, precluding study of alcohol responses in earlier developmental periods. The results support prior work showing high alcohol-induced stimulation, reward, and craving in heavy drinkers or alcoholics (33,79,80), as well as low alcohol-induced sedation and cortisol in other at-risk drinkers (81). However, heavy drinkers have also shown reduced alcohol-related stimulation and ventral striatal brain activation relative to social drinkers (82). Significant methodological differences across studies, i.e., sample size, subject characteristics, alcohol dose, route of administration, and degree of naturalism to usual contexts (16,83), hamper direct comparisons to discern the source of this discrepancy. Thus, while the present study includes one of the largest samples to date and the only investigation of alcohol responses over time, replication will be a necessary next step to assure confidence in the main findings.

In summary, alcohol responses were examined in a unique longitudinal framework in heavy drinkers and light drinker

control subjects. Alcohol response differences between these groups observed at initial testing remained 5 to 6 years later, with greater alcohol stimulating and rewarding effects and lower sedation and cortisol excretion in heavy drinkers. The leading theories of addiction based on animal models were tested in this direct repeated alcohol challenge investigation. Empirical evidence was provided for the early stage of addiction in the allostasis theory with continued heightened alcohol stimulation and reward sensitivity in heavy drinkers with increasing AUD symptoms during the transition of young to early-middle adulthood. These sustained pleasurable effects may increase the drive for excessive drinking (34) despite mounting consequences and alcohol problems. At the same time, heavy drinkers with low AUD symptoms indicative of less harmful drinking over time exhibited reduced alcohol stimulation at re-examination, while heavy drinkers with intermediate AUD symptoms were largely intermediate on their alcohol responses, i.e., in between the low and high AUD groups in alcohol sensitivity. The combination of changes observed supports alcohol response phenotype as an important factor in the development and continuation of excessive drinking and may inform future prevention and intervention approaches. While there are multiple pathways to development of a disorder as complex as AUD, maintenance of alcohol stimulatory and rewarding effects and lower sedative and neuroendocrine responses should be further examined as potential important pathways underlying development and progression of alcohol addiction processes.

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