Predictors of Patterns of Alcohol-Related Blackouts Over Time in Youth From the Collaborative Study of the Genetics of Alcoholism: The Roles of Genetics and Cannabis

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ABSTRACT. Objective: Alcohol-related blackouts (ARBs) are anterograde amnesias related to heavy alcohol intake seen in about 50% of drinkers. Although a major determinant of ARBs relates to blood alcohol concentrations, additional contributions come from genetic vulnerabilities and possible impacts of cannabis use disorders (CUDs). We evaluated relationships of genetics and cannabis use to latent class trajectories of ARBs in 829 subjects from the Collaborative Study of the Genetics of Alcoholism (COGA). **Method:** The number of ARBs experienced every 2 years from subjects with average ages of 18 to 25 were entered into a latent class growth analysis in Mplus, and resulting class membership was evaluated in light of baseline characteristics, including CUDs. Correlations of number of ARBs across assessments were also compared for sibling pairs versus unrelated subjects. **Results:** Latent class growth analysis identified ARB-based Classes 1 (consistent low = 42.5%), 2 (moderate low = 28.3%), 3 (moderate high = 22.9%), and 4 (consistent high = 6.3%). A multinomial logistic regression analysis within latent class growth analysis revealed that baseline CUDs related most closely to Classes 3 and 4. The number of ARBs across time correlated .23 for sibling pairs and -.10 for unrelated subjects. **Conclusions:** Baseline CUDs related to the most severe latent ARB course over time, even when considered along with other trajectory predictors, including baseline alcohol use disorders and maximum number of drinks. Data indicated significant roles for genetic factors for alcohol use disorder patterns over time. Future research is needed to improve understanding of how cannabis adds to the ARB risk and to find genes that contribute to risks for ARBs among drinkers. (*J. Stud. Alcohol Drugs, 78,* 39–48, 2017)

HEAVY DRINKING AND ASSOCIATED consequences are common, costly, and potentially dangerous (Rehm et al., 2007). In most Western societies, heavy episodic, or binge, drinking is likely to develop in the mid-to-late teens and to continue at least into early adulthood (Brown et al., 2008; Mason & Spoth, 2012). A common and important correlate of such heavy alcohol consumption is an alcohol-related blackout (ARB), which has been experienced by 50% of drinkers, including 30% of college students over the previous year (Barnett et al., 2014; Mundt et al., 2012; Schuckit, et al., in press; White et al., 2002; Wilhite & Fromme, 2015). This is a form of anterograde amnesia in which drinkers have problems remembering all (en bloc ARB) or part (fragmentary ARB) of events that occurred when they were conscious, consuming alcohol, and able to perform simple tasks (Marino & Fromme, 2015; Wilhite & Fromme, 2015).

As might be expected for phenomena associated with heavy drinking, ARBs carry enhanced risks for additional adverse events. These include unsafe or unwanted sex, rape and other forms of violence, moodiness and suicidal behaviors, physical injury, continued heavy drinking and the development of alcohol use disorders (AUDs), and early death (Anthenelli et al., 1994; Bae et al., 2015; Hingson et al, 2016; Jennison & Johnson, 1994; Mundt & Zakletskaia, 2012; Pressman & Caudill, 2013; Read et al., 2013; Valenstein-Mah et al., 2015; White et al., 2004). An impaired ability to remember problematic behaviors that occurred during intoxication could also interfere with recognizing the need to avoid future heavy drinking (Wilhite & Fromme, 2015).

ARBs are most likely if blood alcohol concentrations (BACs) are high and rapidly rising. BACs of about .14 g/dl are usually required for fragmentary ARBs, whereas en bloc memory lapses are most likely to be observed at .20g/dl or more (Mundt et al., 2012; White, 2002). However, there are large individual variations regarding the BACs associated with these anterograde memory lapses, with some

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reports that aspects of ARBs can develop at .06 g/dl and others noting that some very heavy drinkers deny ever experiencing these phenomena (Anthenelli et al., 1994; Perry et al., 2006; Wetherill & Fromme, 2016). Although the magnitude of the BAC and the rapidity of the rise of blood alcohol contribute to the ARB risk, they do not explain the entire picture (Marino & Fromme, 2016; Wetherill & Fromme, 2016). Other characteristics potentially related to the ARB risk include demography (e.g., European American ethnicity, older age, and female sex), familial and potentially genetically related influences, and alcohol practices (e.g., higher alcohol intake, earlier drinking onset, and lower levels of response to alcohol) (Jennison & Johnson, 1994; Schuckit et al., 2015; Schuckit et al., in press; Wetherill & Fromme, 2009, 2016; Wetherill et al., 2012). Environmental, personality, and attitudinal characteristics such as heavy drinking peers, externalizing characteristics, and positive expectations of alcohol's effects have also been reported to relate to heavier drinking and/or ARBs (Merrill et al., 2014; Rose & Grant, 2010; Schuckit et al., 2015). Several internalizing characteristics (e.g., drinking to diminish negative moods and stress) (Karg et al., 2011) may be related to depressive symptoms and to heavier drinking and might relate to ARBs.

As highlighted in a recent review (Wetherill & Fromme, 2016), several characteristics that might contribute to differences in vulnerabilities toward ARBs require further investigation—namely, familial and/or genetic factors and concomitant drug use. Regarding familial and genetic factors, family histories of AUDs and a person's prior alcohol-related memory lapses both predict ARBs that occur at lower BACs and/or characterize individuals who demonstrate greater degrees of contextual memory impairment with alcohol (LaBrie et al., 2011; Marino & Fromme, 2015; Nelson et al., 2004; Wetherill & Fromme, 2011; Wilhite & Fromme, 2015). Brain activation patterns during drinking also differ in subjects with and without histories of ARBs, with some evidence that neurobiological characteristics might identify nondrinking youth who later go on to experience ARBs (Marino & Fromme, 2016; Wetherill et al., 2012, 2013). Thus, it is not surprising that a twin study indicated heritability for repeated ARBs of 58%, with some of the genetic load unique to blackouts and a portion that might overlap with the frequency of intoxication, the level of response to alcohol, and variations in alcohol dehydrogenase (Nelson et al., 2004).

The impact of other drug use is another important area of research that needs expansion (Wetherill & Fromme, 2016). Cannabis use may be particularly important to consider because approximately 35% of young adults have used cannabis in the previous year (Haas et al., 2015; Johnston et al., 2014), with reports that 23%–30% of cannabis users have concomitantly used alcohol (Brière et al., 2011; Terry-McElrath et al., 2013). Cannabis by itself diminishes anterograde memory, potentially via impaired hippocampal activity (Batalla et al., 2013; Grant et al., 2003; Meier et al., 2012; Ranganathan & D'Souza, 2006; Solowij et al., 2002; Volkow et al., 2014). As both cannabis use and heavy drinking relate to smoking (Buu et al., 2014), nicotine use was also considered in our analyses. Taken together, these data support the hypothesis that cannabis ingestion during drinking might increase the probability of an ARB.

Considering the plethora of characteristics that relate to ARBs and the complexities of their relationships over time, longitudinal studies using multivariate statistical approaches are logical ways to evaluate how the multiple domains relate to each other in contributing to the ARB risk (e.g., Jennison & Johnson, 1994; Marino & Fromme, 2016; Schuckit et al., 2015). The current analyses present the results of every-2-year follow-ups of 829 subjects in the youth panel from the Collaborative Study of the Genetics of Alcoholism (COGA; Schuckit et al., 2014). The data were used to test three hypotheses: (a) reflecting the high prevalence of AUDs in COGA families, the rates of ARBs will be higher than in most U.S. populations and will increase with age; (b) a latent class growth analysis (LCGA) with an associated multinomial logistic regression analysis will identify distinct classes of trajectories of the number of ARBs over time; and (c) focusing on drinkers' (i.e., individuals at risk for ARBs) repetitive use of cannabis and family histories of AUDs will add significantly to baseline drinking patterns and additional baseline predictors in characterizing the LCGA classes with the highest rates of alcohol-related memory lapses over time.

Method

Sample

Following approval by Human Subjects' Protections Committees at each COGA site, individuals for these analyses were chosen from among 1,132 participants enrolled in the 2012 COGA youth panel. Current evaluations were limited to individuals who had consumed alcohol at each assessment and were evaluated in at least two of four possible periods, yielding 833 participants, of whom 829 had usable data. Of these, 52.5% were nieces or nephews of original COGA probands, 20.7% were offspring, 12.3% were grandchildren, 2.8% were siblings, and the remainder were cousins or individuals who entered the sample through a non–blood relative of the proband (e.g., the spouse of someone from that family). The original COGA probands, recruited more than two decades ago, were alcohol-dependent men and women from alcohol treatment programs who reported multiple alcoholic relatives, as well as comparison subjects chosen through drivers' license applications, visits to medical clinics, and respondents to questionnaires at a university (Bucholz et al., 1994).

Baseline and follow-up assessments for items highlighted in the introduction

At baseline for the drinkers in this evaluation (M_{age} = 18), the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) standardized interview was used to gather information on demography, alcohol, cannabis and additional drug use patterns and problems, as well as externalizing and internalizing conditions. Substance-related disorders, including cannabis use disorders (CUDs), were based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994). SSAGA sensitivities and specificities for most diagnoses range from 75% to 90%, with positive and negative predictive values and retest reliabilities in a similar range (Bucholz et al., 1994; Hesselbrock et al., 1999). The family history of AUDs was based on separate COGA interview data gathered from the parents of the subjects, with imputed data if a parental interview had not been performed.

Levels of response to alcohol at baseline were the average standard number of drinks (10–12 g of ethanol) required for up to four effects (feeling any effect, slurring speech, unsteady gait, or unintended falling asleep) the first five times of drinking using the Self-Rating of the Effects of Alcohol Questionnaire (SRE; Schuckit & Smith, 2006; Schuckit et al., 2007). This measure of alcohol sensitivity has repeat reliabilities of .70–.82, with a higher number of drinks needed for effects indicating a lower level of response per drink (Ray et al., 2011; Schuckit et al., 2007). SSAGA questions for ARB occurrences were: "Have you ever had blackouts when you did not pass out while drinking, but drank enough so that the next day you could not remember things you had said or done?" and "How many ARBs did you have since your prior follow-up?"

Baseline externalizing and internalizing characteristics were measured using the Neuroticism and Conscientiousness scales of the NEO-Five Factor Inventory (McCrae & Costa, 2010), the Barratt Impulsiveness Scale (Stanford et al., 2009), and the Zuckerman Sensation Seeking Scale for those age 18 or older (Zuckerman, 1978) and the Sensation Seeking Scale for Children for younger subjects (Russo et al., 1993). Environmental characteristics and attitudes included the perceived number of peer drinks per occasion using the Important People and Activities Scale (Longabaugh et al., 2001), the sum for positive expectations of the effects of alcohol from the adult and child forms of the Alcohol Expectancy Questionnaire (Goldman, 2002), and drinking alcohol to deal with stress using the total score from a modified Drinking to Cope Scale (Carver et al., 1989; Park et al., 2002).

Analyses

The primary analysis began by entering the count of the number of ARBs reported in the 2 years before each follow-up as dependent variables into an LCGA negative binomial analysis in Mplus (Muthén & Muthén, 2015), along with 18 baseline variables from six domains as covariates (i.e., baseline predictors described above). Prior-6-month maximum number of drinks at each assessment was a time-varying covariate to ensure that the ARB was not only a proxy for heavy drinking. The optimal number of classes regarding the pattern of ARBs over time was indicated when the Bayesian information criterion (BIC) did not decrease with additional classes, when the Lo–Mendell–Rubin Adjusted Likelihood Ratio Test (LMR-LRT) became nonsignificant, and when the classes remained interpretable (Nagin & Tremblay, 2001; Schwarz, 1978). Within this single analysis, Mplus also generated a multinomial logistic regression analysis evaluating how the 18 baseline covariates related to class membership. The relationships of baseline items to latent class membership were further evaluated using chi-square for categorical data and using analysis of variance (ANOVA) for continuous variables. A simultaneous-entry negative binomial regression was used to directly compare the relationships of the average maximum number of drinks across time and baseline CUD diagnosis to the number of ARBs across the analyses. Missing values, primarily reflecting results from individuals who had not yet been interviewed at the last follow-up, accounted for 14.5% of the 3,316 data points (four time points for 829 subjects) and were estimated using a maximum likelihood procedure (Collins et al, 2001).

Results

As shown in the first data column of Table 1, at baseline the 829 subjects were 18 years old on average, half were female, and most reported European American ethnicities. Reflecting COGA overall, 66% had a parent with an AUD, and the lifetime rate of DSM-IV AUDs was 30% (although not shown, alcohol abuse and dependence rates were 23% and 7%, respectively). With a first full standard drink consumed at age 15, at baseline participants reported eight as the maximum number of standard drinks consumed on a single occasion in the past 6 months. Although not entered into the Mplus analysis to avoid multicollinearity with the maximum number of drinks per occasion, these subjects had consumed alcohol 1.2 (1.22) times per week in the past 6 months, imbibing an average of 3.3 (3.74) drinks per occasion. These participants reported needing an average of 3.7 drinks to experience up to four effects (their level of response); 34% had smoked at least 100 cigarettes; and 26% had ever met criteria for a CUD, half of whom were dependent. The remaining items in Table 1 present values for externalizing and internalizing symptoms, peer drinking, and environmental/attitudinal characteristics, with *z* scores used to combine adult and adolescent values for sensation seeking and alcohol expectancies.

Table 1. Baseline characteristics for 829 drinking COGA adolescents/young adults across four latent trajectory classes regarding alcohol-related blackouts

Baseline variable	All subjects (N = 829) M (SD) or %	Class 1 Consistent low (n = 352, 42.5%) M (SD) or %	Class 2 Moderate low (n = 235, 28.3%) M (SD) or %	Class 3 Moderate high (n = 190, 22.9%) M (SD) or %	Class 4 Consistent high (n = 52, 6.3%) M (SD) or %	F or χ^2
Demography						
Age, years	18.3 (2.03)	18.3 (2.11)	17.8 (2.08)	18.7 (1.76)	19.4 (1.38)	11.16***
% Female	49.5	54.5	42.1	42.1	75.0	26.38***
% European American	67.6	57.4	66.4	81.6	90.4	46.16***
Alcohol-related history						
% Lifetime AUD	30.3	14.5	23.8	52.1	86.5	167.05***
Age at drinking onset, years	15.0 (2.30)	15.6 (2.26)	14.9 (2.07)	14.5 (2.51)	14.1 (1.95)	15.12***
Maximum quantity (6 months)	8.0 (6.14)	5.4 (4.75)	7.5 (5.73)	12.0 (6.13)	12.8 (6.20)	86.60***
First 5 SRE [LR]	3.7 (1.84)	3.3 (1.77)	3.7 (1.91)	4.4 (1.75)	4.3 (1.36)	20.66***
% Parental AUD	66.2	60.5	66.8	73.2	76.9	11.92**
Substance-related history						
% Smoked tobacco ≥ 100 times	33.8	25.0	37.9	38.4	57.7	29.01***
% Lifetime CUD	25.9	13.4	28.1	34.7	69.2	87.99***
Externalizing related						
Barratt Impulsivity Score	65.4 (10.55)	62.9 (10.21)	66.2 (10.47)	67.6 (10.13)	70.0 (11.08)	13.34***
Sensation-Seeking Score	0.0 (0.96)	-0.3 (0.96)	0.0 (0.95)	0.4 (0.85)	0.4 (0.88)	22.82***
NEO Conscientiousness	42.9 (10.22)	45.0 (10.63)	42.3 (9.50)	41.1 (9.01)	38.5 (11.67)	10.95***
Internalizing related						
% Ever depressed ≥2 weeks	33.3	27.3	32.8	36.8	63.5	28.16***
NEO Neuroticism	52.0 (9.39)	50.2 (8.82)	53.3 (9.30)	52.7 (9.25)	55.4 (11.80)	8.52***
Environment/attitude measures						
Perceived peer maximum drinks	1.8 (0.91)	1.4 (0.78)	1.8 (0.92)	2.1 (0.90)	2.4 (0.81)	41.79***
Alcohol Expectancy Questionnaire total	0.0 (0.98)	-0.3 (1.00)	-0.0 (0.93)	0.4 (0.81)	0.7 (0.74)	33.69***
Drink to cope	9.9 (3.06)	8.6 (2.17)	10.1 (2.90)	10.7 (3.09)	13.8 (4.00)	63.03***

Notes: COGA = Collaborative Study on the Genetics of Alcoholism; AUD = alcohol use disorder; SRE = Self-Rating of the Effects of Alcohol measure of the number of drinks needed for effects the first 5 times drinking; LR = level of response to alcohol on the SRE; CUD = cannabis use disorder; NEO = NEO Five-Factor Inventory personality inventory with scores presented as T-Scores where 50 indicates an average score regarding the literature; Sensation-Seeking Score = scales z scored within adults and within adolescents; Alcohol Expectancy Questionnaire total = scales z scored within adults and within adolescents. **$p < .01$; ***$p < .001$.

Regarding Hypothesis 1, at baseline for these analyses (about age 18), 30.9% of these drinking subjects had ever experienced an ARB, a figure that increased to 32.9% by age 20, 44.4% by age 23, and 48.9% by age 25. This increase with age was significant (Cochran's Q = 362.2, $p < .001$). Subjects reported an average number of ARBs per 2-year epochs of 2.0 (6.74) (mean and standard deviations) at age 18; 3.8 (16.54) in the 2 years before age 20; 6.6 (21.64) in the period before age 23; and 8.4 (22.03) at average age 25 (comparing ages 18–20, Wilcoxon signed ranks test Z = -0.94, N.S.; for ages 20–23, Z = -9.06, $p < .001$; and for ages 23–25, Z = -5.46, $p < .001$).

As predicted in Hypothesis 2, LCGA identified four ARB latent trajectory classes (Table 1 and Figure 1). Class 1 (consistent low, n = 352) averaged 0–0.1 ARBs every 2 years; Class 2 (moderate low, n = 235) reported 0–10 ARBs per assessment; Class 3 (moderate high, n = 190) noted 3–12 ARBs per period; and Class 4 (consistent high, n = 52) had 18–53 blackouts every 2 years. The LCGA fit statistic for a one-class solution was adjusted BIC = 50,690. For two classes: BIC = 11,060, entropy = .82, probabilities = .96–.96, and LMR-LRT = 682 ($p < .0001$). For three classes, BIC = 10,859, entropy = .77, probabilities = .88–.96, and LMR-LRT = 274 ($p < .02$). The four-class fit statistics were BIC = 10,735, entropy = .81, probabilities = .87–.95, and LMR-LRT = 197 ($p < .0001$). The five-class solution was nonsignificant, with BIC = 10,711, entropy = .83, probabilities = .86–.93, and LMR-LRT = 98 ($p = .09$). The increases over time, using Friedman two-way ANOVA by ranks (3 df), were significant for Class 1 (χ^2 = 81.00, $p < .001$), Class 2 (χ^2 = 425.49, $p < .001$), and Class 3 (χ^2 = 29.03, $p < .001$) and showed a trend for Class 4 (χ^2 = 7.57, $p = .06$).

The five remaining columns in Table 1 demonstrate relationships among baseline characteristics selected from the literature ("covariates" in LCGA) and membership in latent classes. All these baseline characteristics differed significantly across the four latent trajectories.

Recognizing that many baseline variables are related (e.g., level of response with maximum number of drinks, $r = .46$, $p < .001$), Table 2 presents results of a simultaneous-entry multinomial logistic regression analysis within Mplus, with Class 1 (consistent low ARBs) as the comparison group. Here, seven baseline variables significantly related to Class 4 membership (consistent high ARBs) including older age, female sex, baseline AUDs, higher maximum number of drinks, tobacco smoking (a suppressor effect reversed the sign for tobacco smoking as a result of combining smoking, CUD diagnoses and coping in the same analysis), baseline CUD diagnoses (regarding Hypothesis 3), and higher drinking-to-cope scores. The distinction between Class 1 and

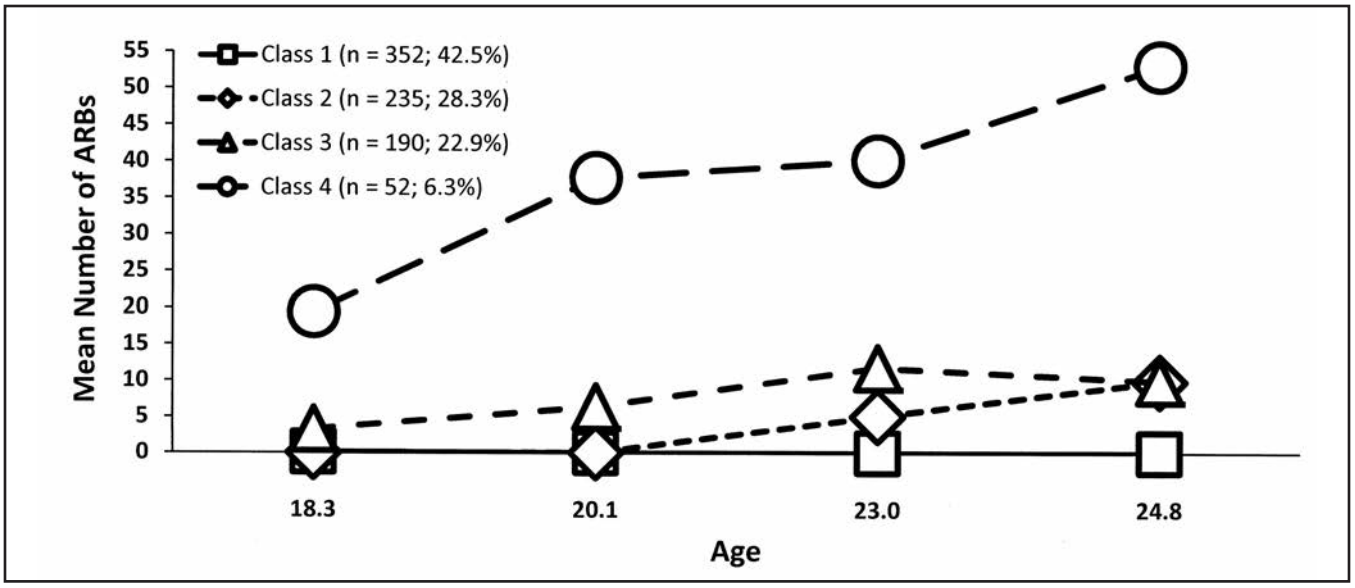

FIGURE 1. Mean number of alcohol-related blackout (ARB) occurrences at each assessment between ages 18 and 25 for 829 Collaborative Study on the Genetics of Alcoholism adolescent and young adult men and women. Trajectories are shown for Class 1 (n = 352, 42.5%), Class 2 (n = 235, 28.3%), Class 3 (n = 190, 22.9%), and Class 4 (n = 52, 6.3%).

Class 3 (moderate high) also related to baseline AUDs and high maximum quantities, with additional contributions from lower conscientiousness (indicating higher externalizing) and higher alcohol expectancies, but Class 3 was not distinguished from Class 1 by baseline age, sex, smoking, CUDs (p = .07), or drinking to cope. Finally, Class 2 membership (moderate low ARBs) was related to younger baseline age, higher maximum number of peer drinks, and higher drinking to cope.

Table 3 expands information on relationships of baseline cannabis-related diagnoses to future ARBs when considered along with maximum number of drinks. Here, using Spearman rho correlations, maximum number of drinks correlated with the number of ARBs across four time points at .57 (p < .001), whereas baseline cannabis diagnoses correlated with ARBs at .30 (p < .001). Maximum number of drinks over time correlated with cannabis diagnoses at .30 (p < .001). A simultaneous-entry multiple logistic regression analysis within a negative binomial model, using both maximum number of drinks and cannabis diagnoses predicting the number of ARBs across four evaluations, revealed that both variables contributed to the result.

Hypothesis 3 also predicted that the family history of AUDs would relate to class membership. However, although AUD family history distinguished across the latent classes in Table 1, it did not contribute to the regression analysis for any class in Table 2. Among variables that contributed to Table 2, family history correlated significantly with maximum number of drinks (.09, p < .05), drinking to cope (.15, p < .001), trends for lifetime AUDs (.06, p = .06), and CUDs (.07, p = .052). Last, regarding familial and possible genetic influences for ARBs, the Spearman ρ correlation for the number of ARBs across time among the 150 sibling pairs within the sample was .23 (p = .005), whereas among 64 random pairs of unrelated participants it was -.10 (p = .64); correlations that were significantly different (z = 2.2, p < .03).

Discussion

This article describes the rates of occurrence and patterns over time for alcohol-related memory lapses in 829 COGA drinkers who were followed from average ages of 18–25 years. Consistent with the literature (Barnett et al., 2014; Mundt et al., 2012; White et al., 2002; Wilhite & Fromme, 2015), by the end of the follow-up almost half of these men and women reported at least one ARB, and 6% demonstrated high levels of persistent ARBs over the years. The analyses were structured to address three hypotheses.

Hypothesis 1 predicted relatively high ARB rates in these subjects, 66% of whom had a parent with an AUD. The current data, however, indicate an ARB prevalence similar to that reported in most U.S. late-adolescent and young-adult samples (e.g., Barnett et al., 2014; Mundt et al., 2012; White et al., 2002; Wilhite & Fromme, 2015), and lower than the 86% rate in a recent study of late adolescents in the United Kingdom (Schuckit et al., 2015). These unexpected results are welcome news in that rates of ARBs were not much higher in these subjects than in most other groups, but, at the same time, alarming in that half of these young subjects drank enough to temporarily impair memory.

A related issue is the relationship of the ARB pattern to the family history of AUDs in Hypothesis 3. Here, as pre-

TABLE 2. Simultaneous-entry multinomial logistic regression analysis beta weights with Class 1 (consistent low) as the reference group and variables in Table 1 as predictors of class membership

Baseline variables	Class 2 Moderate low	Class 3 Moderate high	Class 4 Consistent high
Demography			
Age	-3.07**	0.33	2.26*
% Female	-0.37	1.24	3.04*
% European American	0.48	1.73	1.90
Alcohol relationships			
% Lifetime AUD	-0.42	2.02*	2.83**
Age at drinking onset	0.55	-1.21	-1.50
Maximum quantity (6 months)	1.91	5.15***	2.99**
First 5 SRE [LR]	-0.87	0.38	0.28
% Parental AUD	-0.42	0.50	0.26
Substance-related history			
% Smoked tobacco ≥ 100 times	0.59	-1.23	-2.18*
% Lifetime CUD	1.61	1.84	3.52***
Externalizing related			
Barratt Impulsivity Score	-0.00	-0.97	-0.87
Sensation-Seeking Score	-0.44	0.67	0.01
NEO Conscientiousness	-0.28	-2.04*	-1.60
Internalizing related			
% Ever depressed ≥2 weeks	0.50	1.16	1.43
NEO Neuroticism	1.28	-0.24	-0.99
Environment/attitude measures			
Perceived peer maximum drinks	3.28***	1.43	1.46
Alcohol Expectancy Questionnaire total	-1.43	2.30*	0.93
Drink to cope	2.60**	0.52	3.52***

Notes: AUD = alcohol use disorder; SRE = Self-Rating of the Effects of Alcohol measure of the number of drinks needed for effects the first 5 times drinking; LR = level of response to alcohol on the SRE; CUD = cannabis use disorder; NEO = NEO Five-Factor Inventory personality inventory with scores presented as T-Scores where 50 indicates an average score regarding the literature; Sensation-Seeking Score = scales *z* scored within adults and within adolescents; Alcohol Expectancy Questionnaire total = scales *z* scored within adults and within adolescents.
*$p < .05$; **$p < .01$, ***$p < .001$.

dicted, family history differed across the four latent ARB classes, but family history did not contribute significantly to the multinomial logistic regression. The latter may relate to the significant correlations among family history and other baseline characteristics that also predicted class membership, including maximum number of drinks and drinking to cope. Our data also indicated a greater similarity for the number of ARBs experienced among siblings than among unrelated individuals, indicating at least a familial vulnerability, and a prior twin study (Nelson et al., 2004) reported an ARB heritability of 58%. COGA researchers plan to expand the search for genetic polymorphisms that contribute to vulnerabilities toward ARBs.

Hypothesis 2 proposed that LCGA would identify classes of individuals with different ARB latent trajectories over time. Our analyses identified four latent trajectory classes, with Class 4 demonstrating a pattern of an increasing average of between 18 and 53 ARBs every 2 years across the assessments. The multinomial logistic regression analysis characterized these Class 4 high-risk individuals as likely to be women who were a bit older than the average young adult in the sample, met criteria for both alcohol and cannabis use disorders at baseline, smoked tobacco, and reported using alcohol to cope with stress. Class 3 reported between 3 and 12 ARBs every 2 years, a pattern that was also predicted by baseline AUDs and a relatively high maximum number of drinks, with additional contributions to regression analyses from low conscientiousness and high alcohol expectancies, but that was not predicted by sex, age, cannabis diagnoses, tobacco smoking, or drinking to cope. A combination of relative youth, higher peer maximum number of drinks, and drinking to cope characterized Class 2, with low ARB risks at the first two assessments but an average of 5–10 ARBs every 2 years in the last two assessments.

Although additional study is needed, these results could have implications regarding what to emphasize in prevention programs aimed at decreasing the risk for repetitive ARBs and their associated dangers, especially for individuals with the profiles for Class 4 and Class 3 (Anthenelli et al., 1994; Bae et al., 2015; Hingson et al., 2016; Jennison & Johnson, 1994; Mundt & Zakletskaia, 2012; Pressman & Caudill, 2013; Read et al., 2013; Valenstein-Mah et al., 2015; White et al., 2004; Wilhite & Fromme, 2015). Several groups have described success with programs aimed at decreasing risks for alcohol-related problems in young samples by focusing on predisposing vulnerabilities and associated characteristics to enhance the person's ability to identify his or her risk while also teaching ways to minimize heavy drinking epi-

Table 3. Comparison of relationships of baseline maximum number of drinks and baseline cannabis use disorder (CUD) to the number of follow-up alcohol-related blackouts (ARBs)

Variables	ARB total over 4 times	Maximum drinks mean over 4 times
Spearman ρ correlations		
Maximum drinks mean over 4 times	.57***	
Lifetime CUD baseline [25.9%]	.30***	.30***
Simultaneous-entry negative binomial regression: Odds ratio [95% confidence interval]		
Maximum drinks mean over 4 times	4.58 [3.69, 5.70]***	
Lifetime CUD baseline	2.13 [1.58, 2.88]***	

***$p < .001$.

sodes (Conrod et al., 2013; Schuckit et al., 2016). A similar approach was successfully applied specifically to ARBs (Kazemi et al., 2013).

A second element of Hypothesis 3 was that heavy cannabis use (here measured by a CUD) would be associated with repetitive ARBs, even after other important risk factors such as a high maximum number of drinks were controlled for. As proposed, the prevalence of baseline CUDs increased in a stepwise fashion across the four latent classes from 13% for Class 1 to 69% for Class 4 in Table 1, with cannabis diagnoses contributing significantly to identifying Group 4 and a trend for Group 3 in Table 2. The potential relationship between alcohol and cannabis in producing ARBs and potential underlying mechanisms (e.g., complementary actions on memory through the hippocampus [e.g., Ranganathan & D'Souza, 2006]) will require future direct evaluation in laboratory studies of both human and animal models (Wetherill & Fromme, 2016).

Several additional findings are worth noting. First, most of the present characteristics related to ARBs over time are consistent with prior cross-sectional studies of alcohol-related memory lapses, as described in the introduction. These include key roles of prior heavier drinking and other substance use, a European American background, externalizing characteristics, heavier drinking peers, higher positive alcohol expectancies, and using alcohol to cope with stress. It is interesting that, consistent with several recent studies (e.g., Schuckit et al., 2006, 2015, 2016), the regression analyses did not support a powerful relationship between an alcohol-related adverse outcome and baseline internalizing measures, such as ever feeling depressed for 2 or more weeks, anxiety or depressive diagnoses, or elevated neuroticism scores. This may reflect the bidirectional relationship between heavy drinking and internalizing symptoms (e.g., Bell et al., 2015; Schuckit et al., 2013) as well as between heavy drinking and ARBs, with the result that, when both heavy drinking and internalizing symptoms were entered into the regression in Table 2, mood and anxiety symptoms dropped out as predictors.

As with all studies, it is important to place the current results into perspective. First, the data come from a single study of families with high densities of AUDs, which might limit the generalizability of the results. Second, all information was gathered through self-reports without corroboration from other sources, which may have produced an underreporting of substance-related problems. This could be especially problematic for ARBs, because a person's recognition of experiencing an ARB often requires reports from other individuals who observed the drinking episode. This restriction may have contributed to the absence of internalizing characteristics from the multinomial logistic regression, as depressed individuals may be more likely to drink alone. Third, the items used in these analyses depended on how data were structured within the COGA data set, which had not originally been developed specifically to study ARBs (e.g., defining smoking use as >100 times). Fourth, the baseline measures did not include some other potential correlates of ARBs such as pre-partying and drinking games. Finally, there are concerns regarding the use of mixture modeling, including LCGA, to evaluate individual differences in alcohol use and its consequences (Bauer & Curran, 2003; Nagin & Tremblay, 2005; Sher et al., 2011), including whether such analyses generate spurious classes and whether the final results reveal the most accurate model. Thus, readers need to remember that latent classes may vary depending on the sample evaluated and the specific variables used (Bauer & Curran, 2003; Sher et al., 2011).

In summary, these data demonstrate a potentially important role of repetitive cannabis use (i.e., CUDs) in the development of repetitive ARBs and add to the growing literature supporting a role of genetic factors in the development of ARBs among drinkers. The COGA group will continue to address these leads in future studies.

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