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Associations between adolescent alcohol use and neurocognitive functioning in young adulthood

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ABSTRACT

This study examined the associations between excessive alcohol intake during adolescence and neurocognitive functioning in young adulthood and whether these relations varied by sex. Participants were working-class Chilean adolescents ($N = 692$; M_{age} 16.0 years; 54.5% female) who provided frequency of past 30-day bingeing and past-year intoxication. Neurocognitive measures were completed in young adulthood (M_{age} 21.2 years). Illicit substance users were excluded a priori and other substance use was controlled. When males and females were considered simultaneously, no main effects of intoxication or bingeing were found. However, several sex-specific effects emerged for intoxication, such that more frequent intoxication was associated with poorer visual memory, attention, processing speed, response inhibition, and cognitive flexibility in females, while frequent intoxication related to better attention and processing speed in males. In general, effect sizes were small. No relations emerged for verbal memory, working memory, or spatial learning. Possible factors that contribute to divergent sex effects are discussed.

Adolescence is a critical developmental period during which the human brain undergoes significant structural and functional change (Blakemore, 2012; Casey et al., 2008). As a result of ongoing neuro-maturational development, adolescents are at increased vulnerability to the neurotoxic effects of alcohol (Carbia et al., 2018; Lees et al., 2019, 2020). Neuroimaging studies have identified brain aberrations associated with heavy alcohol use during adolescence, including alterations in gray- and white-matter, cortical thickness, brain connectivity, neural activity, and some indication of neuroinflammation (Ewing et al., 2014; Jones et al., 2018; Luciana et al., 2013). These alterations are known to correspond to poorer attention, memory, and spatial abilities (Spear, 2018; Squeglia et al., 2014). Several cross-sectional studies have identified dose-response associations between binge drinking during adolescence and reduced visuospatial processing, verbal learning, and inhibitory control (reviewed in Carbia et al., 2018; Lees et al., 2019; Spear, 2018). Of the longitudinal studies conducted, most have short length of follow-up ($1-60$ months), are conducted on convenience samples (i.e., Caucasian college students), or are not particularly consistent across studies (Carbia et al., 2018; Lees et al., 2019, 2020). For example, studying a small sample of university students, binge drinking was associated with difficulties in immediate and delayed recall at a 2-year (Mota et al., 2013) and 6-year follow-up (Carbia et al., 2017a, 2017b). However, a study involving a large British cohort found no association between frequent alcohol use from ages 15 to 21 years and impaired working memory at age 24 (Mahedy et al., 2018, 2021).

Previous research also suggests that alcohol may have sex-specific effects (Alfonso-Loeches et al., 2013; Squeglia et al., 2011, 2012, 2014). Systemic reviews of neuropsychological studies involving young binge drinkers have found that while some cognitive domains appear to be differentially impacted by males' and females' alcohol use, other domains appear similarly affected (Lees et al., 2020). For example, poor

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cognitive flexibility, working memory, and visual searching abilities have been found in female binge drinkers, while worse response inhibition and visuospatial memory have been found in male binge drinkers (Carbia et al., 2018; Lees et al., 2019). In contrast, Squeglia et al. (2009) found that more drinking days during adolescence predicted poorer visuospatial memory in females but not in males, and that more hangover symptoms predicted slower speed of processing and shorter sustained attention in males only. Another study found that male binge drinkers scored lower on a short-term memory task than female binge drinkers and non-binge drinking males (Parada et al., 2012). Still others have found that both male and female binge drinkers had equivalent deficits in immediate and delayed recall compared to non-drinking controls (Carbia et al., 2017a). In reviews of the literature, it has been noted that most studies do not examine sex-specific effects, and those that do, often involve very small samples, raising issues of low statistical power (Carbia et al., 2018; Day et al., 2015; Lees et al., 2019). Thus, consistent evidence appears to be currently lacking to support strong decisive conclusions about sex-specific effects of adolescent alcohol use on cognition (Carbia et al., 2018; Lees et al., 2020).

Current study

Aims of the current study were to examine how heavy alcohol intake (intoxication, binge drinking) during adolescence is related to neurocognitive functioning in young adulthood and whether these relations vary by sex. We strove to clarify possible long-term effects (across a 5-year period, or from alcohol use at age 16 to neurocognition at age 21) and to involve a broad range of neurocognitive outcomes. This study included measures of attention, speed of processing, visual-motor integration, spatial learning, response inhibition, cognitive flexibility (task switching), and three aspects of memory (visual, verbal, and working memory). Studying multiple cognitive domains may be useful for identifying specific neuropsychological deficits involved in, and specific brain regions affected by, excessive alcohol use. We examined outcomes associated with both binge drinking and intoxication, the latter of which may reflect a more individualized indicator of alcohol toxicity given that intoxication is affected by body weight, calorie intake at the time of drinking, and a host of additional factors (age, sex, history of drinking, etc.; Spear, 2018), factors not accounted for in binge drinking. Most studies to date examine adolescent binge drinking using the NIAAA definition of bingeing (i.e., having at least five [for male] or four [for females] alcoholic drinks within a 2-hour time frame) (National Institute of Alcohol Abuse and Alcoholism (NIAAA),), 2021). However, subjective sense of intoxication may occur at different levels of alcohol intake and, thus, be a useful additional indicator of alcohol toxicity.

Based on the literature, we hypothesized that more frequent binge drinking and intoxication during adolescence will relate to poorer neurocognitive functioning in young adulthood. Given suggestions in the literature that alcohol may have sex-specific effects, as well as the different neurocognitive performance and frequency of alcohol use among males and females in the current study (described below), we examined whether sex moderates the association between alcohol use and neurocognition. Given the lack of sufficiently powered studies to support definitive conclusions about sex differences in alcohol's effects, no sex-specific hypotheses are offered (Carbia et al., 2018; Lees et al., 2019, 2020).

We addressed study aims within a large longitudinal sample of working-class Chilean youth. Chile is a unique context in which to study effects of heavy alcohol use given that drinking alcohol constitutes a widely accepted behavior in that country. Two-thirds of Chilean youth have used alcohol by age 15 and the average age of first consuming alcohol is 13.7 years (National Service for the Prevention and Rehabilitation of Drug and Alcohol Consumption [SENDA], 2018). Although the minimum legal drinking age for alcohol is 18 years, Chile has been an open-alcohol country where age verification (carding) for alcohol purchase only recently became required (August 12, 2021). Moreover, beer and wine are relatively inexpensive in Chile, contributing to its frequent use (Probst et al., 2018). Not surprisingly, prevalence of teenage alcohol use is higher in Chile than in the U.S. In 2019, 35.9% of American school youth (grades 8, 10, and 12) used alcohol in the past year, with 19.5% reporting intoxication within the past year (Miech et al., 2020). In Chile in 2017, 57.3% of 8th- to 12th-graders reported past-year alcohol use and, among those with past-month use, 61.7% reported having drank five or more drinks on a single occasion in the past 30 days (National Service for the Prevention & Rehabilitation of Drug and Alcohol Consumption (SENDA), 2018).

Methods

Sample and study design

Participants were part of the Santiago Longitudinal Study, which began as a nutrition trial and neuromaturation study of 1,792 infants (Lozoff et al., 2003). Healthy 6-month-old infants were recruited from community clinics serving working-class families in Santiago, Chile. Participants were reassessed at ages 16 and 21 years. A total of 1,112 youth participated at adolescence (ages 11.9 − 19.2 years), with 1,109 participants completing an alcohol use questionnaire (Delva et al., 2015; Sanhueza et al., 2013). To reduce the wide age range, youth age 13 or younger and age 18 or older were omitted ($n = 22$), leaving 1,087 adolescents (M age 16.0, range 14.0 − 17.4). An additional 45 adolescents were omitted due to self-report of illicit substance use within 30 days prior to the alcohol assessment (e.g., use of cocaine, ecstasy, stimulants, sedatives, etc.), netting 1,042 adolescents eligible for analysis. All youth were of Spanish or indigenous descent.

At age 21 ($M = 21.2$ years, $SD = 0.6$), 1,001 participants were studied, of whom 946 completed neurocognitive assessments. Twenty-one participants were excluded from analysis due to self-reported use of illicit substance use within 30 days prior to the 21-year neurocognitive assessment. Of the remaining participants, 692 had alcohol use data at adolescence (as described above). Thus, this study's analytic sample involves 692 participants (54.5% female) who had alcohol use data at adolescence, recently consumed no illicit substances at adolescence or young adulthood, and had neurocognitive outcomes measured at age 21. (Supplementary Figure 1 shows participant flow chart.)

The analytic sample of 692 participants was similar to the individuals who completed the alcohol use assessment at adolescence but were subsequently omitted or lost to follow-up in regard to: age at the adolescent and young adult assessments, socioeconomic status, and maternal IQ (described below). However, compared to the individuals omitted from analyses, the 692 participants studied here were more likely to be female (45.5% vs. 54.5%; $\chi^2 = 40.64$, $p < .001$), had more years of formal education at age 21 (11.8 vs. 12.5; $t = 3.89$, $p = .001$), were less likely to be intoxicated within the last 12 months at adolescence (49.3% vs. 37.8%; $\chi^2 = 16.08$, $p < .001$), and less likely to have binge drank within the last 30 days at adolescence (38.3% vs. 22.8%; $\chi^2 = 13.12$, $p < .001$). These latter differences likely reflect the exclusion of those who reported illicit substance use at adolescence or young adulthood.

Procedures

At both adolescence and young adulthood, youth completed the study questionnaires in a private room at a university research center which was familiar to participants from their earlier study involvement. At the young adult assessment, participants completed the Trail Making Test (described below) and the CogState Brief Battery, which is a computerized testing platform involving cognitive tasks that are adaptations of standard neuropsychological tests (CogState.com; Maruff et al., 2009). The full test battery requires approximately 60 minutes to complete. Spanish versions of the study's neurocognitive measures were supplied by each measure's publisher, and tests were administered by psychologists trained in the administration of such tests and according to standard instructions. All study components were approved by the relevant university institutional review boards in the U.S. and Chile (IRB Project Number #121649). At the adolescent assessment, signed informed consent was obtained from parents and assent was obtained from adolescents. Participants provided informed written consent at the young adult assessment.

Measures

Adolescent alcohol use

Questions about alcohol use were embedded in a larger questionnaire asking about use of various substances. Individuals were first asked if they had ever consumed alcohol in their lifetime, and if affirmative, if they had drank alcohol within the last 30 days. Those who responded affirmatively were asked how many times they "had five or more drinks (wine, beer, liquor) in one sitting within the last 30 days" and, separately, how many times they "had four or more drinks (wine, beer, liquor) in one sitting within the last 30 days." Response options ranged from 0 to 14 times, with an additional option of 15 = binged 15 or more times. In accordance with National Institute of Alcohol Abuse and Alcoholism (NIAAA) (2021) guidelines, males' responses to drinking 5 or more drinks on one occasion and, females' responses to drinking 4 or more drinks on one occasion, were used to index frequency of binge drinking.

Participants also responded whether they had drank alcohol within the last 12 months. If affirmative, they were asked whether they had "ever drank enough alcohol to get drunk?" Those who answered affirmatively were asked "how many occasions have you been drunk or high from drinking alcoholic beverages within the last 12 months?" Response options were: 0 = never, 1 = 1 or 2 occasions, 2 = 3 to 5 occasions, 3 = 6 to 9 occasions, 4 = 10 to 19 occasions, 5 = 20 to 39 occasions, and 6 = 40 or more occasions.

Neurocognitive outcomes at young adulthood

The **CogState Neuropsychological Test Battery (CogState)** consists of computerized cognitive tasks that assess memory, visual attention, learning, and task switching (CogState.com; Maruff et al., 2009). The tests are unaffected by language and cultural differences, demonstrate minimal repeated learning effects, and are sensitive to subtle memory and learning impairments found in clinical or aged populations (Buckley et al., 2017). Performance is measured by number of correct responses, erroneous responses, or speed. The current study administered the following CogState tests: (1) *One-Card Back* test, which is a one-back working memory task (scored as number of errors); (2) *One-Card Learning* test assesses short-term visual memory (number of errors); (3) *Paired Associated Learning* test assesses visual memory in a card matching scenario (number of errors); (4) *International Shopping List* assesses verbal memory (scored as number correct); (5) *Groton Maze Learning task* measures spatial learning efficacy in a maze-grid format (number of errors), and; (6) *Detection task* is a choice reaction time test involving visual-motor integration skills and assesses visual attention and speed of processing (scored in $\log_{10}$ transformed milliseconds and converted back to milliseconds for purposes of a meaningful metric). Detailed description of each test is provided in the Supplemental Material.

The **Trail Making Test (TMT)** assesses visual-motor integration, cognitive flexibility, and response inhibition in a visual searching and sequencing task (Sánchez-Cubillo et al., 2009). Part A of the test involves drawing lines between numbered circles in consecutive order (from 1 to 25) as quickly as possible and tests visual-motor integration. Immediately thereafter, participants are asked to rapidly draw lines connecting numbers and letters in alternating order (1 to A to 2 to B etc.; Part B). The increased demands of Part B assess the ability to inhibit a triggered response (to effortfully suppress a prepotent response) and to alternate between different response sets (set shifting) (Arbuthnott & Frank, 2000; Gaudino et al., 1995). Performance is assessed as total time (in seconds) to complete Parts A and B correctly, with longer times indicating poorer performance. Time taken to complete Part B minus Part A is used to assess response inhibition void of processing speed and is thought to reflect a pure index of cognitive flexibility (Sánchez-Cubillo et al., 2009).

Covariates

Covariates determined *a priori* to relate to study outcomes included family socioeconomic status (SES; measured using the Graffar social class instrument; Mendez-Castellano & de Mendez, 1986) and maternal IQ (abbreviated Wechsler Adult Intelligence Scale; Wechsler, 1955). These variables were drawn from data collected during participants' infancy as there were little missing data at that time point and little change across time in these variables. The following additional covariates were included: age at the adolescent assessment, marijuana and, separately, cigarette use within the last 30 days of the adolescent assessment (yes, no), marijuana, cigarette, and alcohol use within 30 days of the young adult assessment (yes, no), and years of formal education at the young adult assessment. Age at first alcohol use and age at the young adult assessment were initially considered as covariates but were not associated with any study variable and not considered further.

Data analysis

A series of multivariable linear regressions were fit to the data, with neurocognitive scores regressed on frequency of intoxication and, in separate models bingeing, controlling for sex and covariates. Additional models were computed incorporating the sex x intoxication (or bingeing) interaction. Sex was represented as a binary variable, coded as male = 1, female = 0. Frequency of intoxication and bingeing were mean-centered. Unstandardized regression coefficients, adjusted for covariates, are reported. Significant sex x intoxication (or sex x bingeing) interactions were plotted using the unstandardized predicted variables from the regressions, and the slopes for males and females are noted. There was no multicollinearity among the predictors (variance inflation factors ≤ 1.2). Prior to conducting analyses, we assessed normality of the neurocognitive scores. Once outliers were omitted, all scales showed normal distribution (Tabachnick et al., 2007). *P* values were adjusted to control for family-wise error associated with multiple testing using the Benjamini-Hochberg correction method and the false discovery rate of 5% (Benjamini & Hochberg, 2000).

Frequency of intoxication was coded as: 0 = never drank alcohol ($n = 233$), 1 = drank alcohol but not been intoxicated within last 12 months ($n = 196$), 2 = intoxicated once or twice within the last 12 months ($n = 69$), 3 = intoxicated 3 to 5 times within the last 12 months ($n = 138$), and 4 = intoxicated 6 or more times within the last 12 months ($n = 54$). Frequency of binge drinking (as defined by NIAAA for males and females) was coded as: 0 = never drank alcohol ($n = 233$), 1 = drank

Table 1. Descriptive statistics of participant characteristics and study variables.

Variable	N	*M* or %	*SD*	Range
Assessed at infancy:				
Sex (% female)	692	54.5%		
†Socioeconomic status[a]	692	27.1	6.2	11 – 47
†Maternal IQ	692	84.2	9.3	52 – 110
Assessed at adolescence:				
†Age, years	692	16.0	1.0	14.0 – 17.4
Drank alcohol last 12 m	692	66.3%		
Intoxicated last 12 m	690	37.8%		
Frequency intoxicated last 12 m[b]	396	2.1	1.0	1 – 6
Binge drank last 30d[c]	692	22.8%		
Frequency binge drank last 30d[d]	158	3.2	3.4	1 – 15
†Marijuana use last 30d	692	23.0%		
†Cigarette use last 30d	692	29.0%		
Assessed at young adulthood:				
Age, years	692	21.2	0.6	20.8 – 24.8
†Years formal education	692	12.5	1.6	5 – 15
†Alcohol use last 30d	692	64.5%		
†Marijuana use last 30d	692	26.7%		
†Cigarette use last 30d	692	45.3%		
Neurocognitive measures at age 21				
One card back, working memory, err	690	4.29	6.4	0 – 25
One card learning, visual s-t memory, err	691	28.2	9.4	5 – 55
Paired associations, visual memory, err	690	16.3	19.1	0 – 66
Int shopping list, verbal memory, corr	692	26.4	3.8	13 – 35
Groton maze task, spatial learning, err	692	48.3	15.7	17 – 107
Detection, visual attention/sop, msec	690	438.8	14.0	223 msec – 1.0 sec
TMT Part A, vis-motor integration, sec	603	43.9	16.5	16 – 119
TMT Part B, response inhibition, sec	601	82.6	36.7	20 – 289
TMT B – A, cognitive flexibility,[e] sec	601	39.4	32.2	0 – 136

Note. last 12 m = last 12 months. last 30d = last 30 days. s-t = short-term. Err = number of errors. corr = number correct. sop = speed of processing. msec = milliseconds. sec = seconds. TMT = Trail Making Test. † Indicates a covariate. [a] Higher scores indicate more socioeconomic disadvantage. [b] 1 = intoxicated on 1 or 2 occasions last 12 m, 2 = 3 to 5 occasions, 3 = 6 to 9 occasions, 4 = 10 to 19 occasions, 5 = 20 to 39 occasions, 6 = 40 or more occasions. [c] Defined as: 5 or more drinks on one occasion for males, and 4 or more drinks on one occasion for females. [d] 1 = binged once last 30d, 2 = two times, 3 = three times … 15 = binged 15 or more times in last 30d. [e] Response inhibition void of processing speed.

alcohol but not binged within last 30 days ($n = 301$), 2 = binged once within the last 30 days ($n = 114$), and 3 = binged 2 or more times in last 30 days ($n = 44$).

Results

Alcohol use and sex differences

Of the adolescents studied, 66.3% had drank alcohol within the past 12 months, 37.8% had been intoxicated at least once during the past year, and 22.8% had binge drank within the past 30 days (Table 1). More males than females drank alcohol within the last year, had been intoxicated in the last year, and had binge drank within the past 30 days (Table 2). Among those who drank within the past year, males reported being intoxicated more frequently than females, but frequency of past-month binge drinking was equivalent for males and females. Frequency of alcohol bingeing and intoxication were positively correlated (males, $r = .49$, $p < .001$; females, $r = .51$, $p < .001$). Compared to females, males were slightly older at young adulthood, had fewer years of education, and reported more past 30-day use of alcohol, marijuana, and cigarettes at young adulthood (Table 2). Regarding the neurocognitive tests, compared to females, males had poorer verbal memory (International Shopping List), better spatial learning (Groton Maze), better visual attention/faster speed of processing (Detection), poorer response inhibition (TMT Part B), and poorer cognitive flexibility (TMT B – A) (Table 2).

Regression results

Results of the regressions (excluding the sex interaction term and controlling for sex, the covariates, and family-wise error) showed no main effects of intoxication or bingeing on any of the neurocognitive test scores (Table S1) Models involving intoxication and the sex x intoxication interaction indicated three effects associated with sex (Table 3; International Shopping List, Groton Maze Learning, and Detection), all of which were consistent with the mean differences shown in Table 2. One significant intoxication effect was found for the One Card Learning visual short-term memory task. Given the binary coding of sex as female = 0, this result indicates that for every one-unit increase in frequency of intoxication, girls' visual

Table 2. Participant characteristics and study variables by sex.

	Male[a] (n = 270-315)		Female[b] (n = 314-377)		
	M or %	*SD*	*M* or %	*SD*	t or χ^2
†Socioeconomic status[c]	26.9	6.2	27.2	6.2	0.63
†Maternal IQ	84.0	9.5	84.4	9.2	0.61
Assessed at adolescence:					
†Age, years	16.0	1.0	16.0	1.0	0.06
Drank alcohol last 12m	70.4%		62.1%		8.90**
Intoxicated last 12m	44%		32%		6.95**
Frequency intoxicated last 12m[d]	2.2	1.0	1.9	0.8	3.41***
Binge drank last 30d[e]	27.3%		18.4%		3.92*
Frequency binge drank last 30d[f]	3.1	3.5	3.5	3.3	0.56
†Marijuana use last 30d	23%		24%		0.94
†Cigarette use last 30d	28.3%		31.6%		1.13
Assessed at young adulthood:					
Age, years	21.2	0.7	21.1	0.5	1.89*
†Years formal education	12.3	1.7	12.6	1.6	2.36*
†Alcohol use last 30d	73.6%		55.9%		4.99***
†Marijuana use last 30d	34.8%		21.2%		4.37***
†Cigarette use last 30d	51.2%		40.0%		2.47**
Neurocognitive outcomes at age 21					
One card back, errors	4.1	6.5	4.4	6.2	0.60
One card learning, errors	27.9	9.5	28.5	9.3	0.92
Paired associations, errors	15.9	17.9	16.3	20.9	0.25
Int shopping list, corr	25.4	3.9	27.2	3.5	6.28***
Groton maze, errors	46.3	14.6	50.0	16.5	3.09**
Detection, msec	424.3	13.9	455.1	14.2	26.96***
TMT Part A, sec	43.1	14.8	44.6	17.7	1.13
TMT Part B, sec	85.6	42.7	80.2	31.0	1.80*
TMT Part B − A, sec	43.0	37.5	36.5	27.1	2.46*

Note. Last 12 m = last 12 months. Last 30d = last 30 days. corr = number correct. msec = milliseconds. sec = seconds. TMT = Trail Making Test. † Indicates a covariate. [a] Ns for males ranged from 309-315 for alcohol and CogState measures, and 270-278 for TMT measures. [b] Ns for females ranged from 370-377 for alcohol and CogState measures, and 314 – 325 for TMT measures. [c] Higher scores indicate more socioeconomic disadvantage. [d] 1 = intoxicated on 1 or 2 occasions, 2 = 3 to 5 occasions, 3 = 6 to 9 occasions, 4 = 10 to 19 occasions, 5 = 20 to 39 occasions, 6 = 40 or more occasions. [e] Defined as: 5 or more drinks on one occasion for males, and 4 or more drinks on one occasion for females. [f] 1 = binged once last 30d, 2 = two times, 3 = three times … 15 = binged 15 or more times in last 30d. *$p < .05$. **$p < .01$. ***$p < .001$.

short-term memory errors increased by 1.37 ($\beta = .13$, $p < .05$). Intoxication was unrelated to boys' visual memory errors ($\beta = -.03$).

Significant sex x intoxication interactions were found for Paired Associations (visual memory), Detection (attention/speed of processing), TMT Part B (response inhibition), and TMT B—A (cognitive flexibility). (Plots of male and female test scores by intoxication frequency are shown in Figure 1). Results indicated that, for the Paired Associations test, for every one-unit increase in intoxication frequency, girls made 3.25 more errors (slope $\beta = .13$, $p < .05$), while boys made 0.12 fewer errors ($\beta = -.01$) (Table 3). Contrasting the estimated means at each level of intoxication revealed that girls made significantly more errors than boys at the most frequent level of intoxication (intoxicated 6 or more times in the past year). Results for the Detection test indicated that for every one-unit increase in intoxication, boys' reaction time decreased (was faster) by 104 msec ($\beta = -.20$, $p < .01$), while girls' reaction time increased (was longer) by 101 msec ($\beta = .13$, $p < .05$). Contrasting the estimated means at each level of intoxication revealed that males and females diverged significantly at the frequency mark of intoxicated 3 to 5 times in the past year. Results for TMT Part B indicated that for every one-unit increase in intoxication frequency, girls' completion time increased by 6.7 sec ($\beta = .20$, $p < .01$), while boys' completion time decreased by 1.6 sec ($\beta = -.02$). Males and females diverged significantly at the intoxicated '6 or more times' frequency mark. Results for TMT B—A indicated that girls' completion time increased by 6.2 seconds ($\beta = .16$, $p < .05$), while boys' completion time decreased by 1.1 sec ($\beta = -.01$) for every one-unit increase in intoxication frequency. Males and females differed on the TMT B—A at both the 'never drank' mark and the 'intoxicated 6 or more times' mark. (Full models with covariates are shown in Table S2).

Results of regressions involving bingeing indicated one sex x bingeing interaction (for TMT B—A [$B = -6.89$, SE $= 3.26$, $p < .05$]), but this effect was nonsignificant when controlling for family-wise error (Table S3; full models shown in Table S4).

Discussion

This study found that, when considering males and females simultaneously, neither intoxication nor

Table 3. Effect of sex and intoxication on neurocognitive functions in young adulthood.

	B	*(SE)*
One card back, working memory, err		
Sex	−0.08	(0.46)
Intoxication	0.68	(0.36)
Sex x Intoxication	−0.78	(0.47)
One card learning, visual s-t memory, err		
Sex	−0.74	(0.75)
Intoxication	1.37*	(0.58)
Sex x Intoxication	−1.50	(0.77)
Paired associations, visual memory, err		
Sex	−3.18	(1.61)
Intoxication	3.25*	(1.23)
Sex x Intoxication	−3.37*	(1.61)
Int shopping list, verbal memory, corr		
Sex	−1.30**	(0.30)
Intoxication	0.103	(0.23)
Sex x Intoxication	0.452	(0.31)
Groton maze learning, spatial learning, err		
Sex	−5.04**	(1.30)
Intoxication	1.65	(1.00)
Sex x Intoxication	−1.73	(1.32)
Detection, visual attent/sop, msec		
Sex	−115**	(10)
Intoxication	101	(10)
Sex x Intoxication	−205*	(10)
TMT Part A, visual-motor integ, sec		
Sex	−.702	(1.46)
Intoxication	.565	(1.12)
Sex x Intoxication	−1.20	(1.49)
TMT Part B, response inhibition, sec		
Sex	4.67	(3.12)
Intoxication	6.65*	(2.39)
Sex x Intoxication	−8.24*	(3.16)
TMT Part B − A, cog flex, sec		
Sex	5.49	(2.91)
Intoxication	6.19*	(2.23)
Sex x Intoxication	−7.25*	(2.94)

Note. Sex coded as female = 0, male = 1. Intoxication indicates frequency of intoxication during past 12 months during adolescence, coded as: 0 = never drank alcohol, 1 = has used alcohol, not intoxicated last 12 m, 2 = intoxicated once or twice within last 12 m, 3 = intoxicated 3 to 5 times last 12 m, 4 = intoxicated 6 or more times last 12 m. s-t = short-term. err = number of errors. corr = number correct. sop = speed of processing. msec = milliseconds. sec = seconds. TMT = Trail Making Test. Ns for the CogState results ranged from 690 to 692 and from 601 to 603 for the TMT results. All models included several covariates (full models shown in Table S1). All *p* values were adjusted for family-wise error. **p* < .05. ***p* < .01.

bingeing during adolescence were related to any of this study's neurocognitive scores. However, several sex-specific effects were found for intoxication, such that adolescent girls who were frequently intoxicated were more likely to have poorer visual memory, attention, processing speed, response inhibition, and cognitive flexibility 5 years later than girls who were never or infrequently intoxicated during adolescence. Very few effects emerged for boys, with boys who reported frequent intoxication having better visual attention and speed of processing in young adulthood. In general, despite the statistically significant interactions, the effect sizes were relatively small, suggesting that frequent intoxication conferred only slight decrements in girls', or gains in boys', cognitive functions. Moreover, for the most part, the test performance of males and females diverged only at the most frequent level of intoxication (6 or more times within the past year), with only performance on the Detection test diverging when males and females were intoxicated 3 to 5 times or more often in the past year. The current findings are consistent with prior studies that show poorer visual memory (Vinader-Caerols et al., 2017), attention and visual processing (Nguyen-Louie et al., 2015), cognitive switching (Winward et al., 2014), and inhibition (Jones et al., 2017; Winward et al., 2014) among adolescent binge drinkers, with these studies either not testing or not finding sex differences. The current results add to these findings by clarifying that such adverse effects pertain only to females, persist into early adulthood, and stem from adolescent intoxication and not bingeing.

The effects found for intoxication may impact several areas in young women's lives. For example, effects related to poorer visual memory may portend to difficulties in most academic tasks, including spelling, reading, and math (Silver et al., 2007). Poor response inhibition could impinge on thoughtful decision-making and self-regulation skills and contribute to impulsive behaviors (Van den Wildenberg & Crone, 2005). Effects associated with poor cognitive flexibility might relate to limits in adaptive problem solving and ability to complete various tasks simultaneously (Peters & Crone, 2014). Poor attention and processing speed could interfere with such basic tasks as driving. These ramifications are particularly significant given that there has been a dramatic increase in prevalence of alcohol consumption in women ages 18 and older in both Chile and the U.S., with 42.5% of Chilean women and 69% of American women drinking alcohol in the last month (Dawson et al., 2015; Leyton & Arancibia, 2016).

In the current study, adverse effects due to frequent intoxication pertained exclusively to females, with one favorable effect found for males. Several factors have been discussed as possibly contributing to such sex-specific effects. For example, Squeglia et al. (2011) found that, when compared to female nondrinkers, female binge drinkers exhibited reduced neural activation in the frontocortical brain region during an executive function task, with lower neural activation linked to poorer visual tracking and sustained attention. In contrast, adolescent male binge drinkers in that study exhibited greater neural activation in the frontal brain region than male controls, with greater activation in that site correlated with better visual-motor integration and visual attention. This is

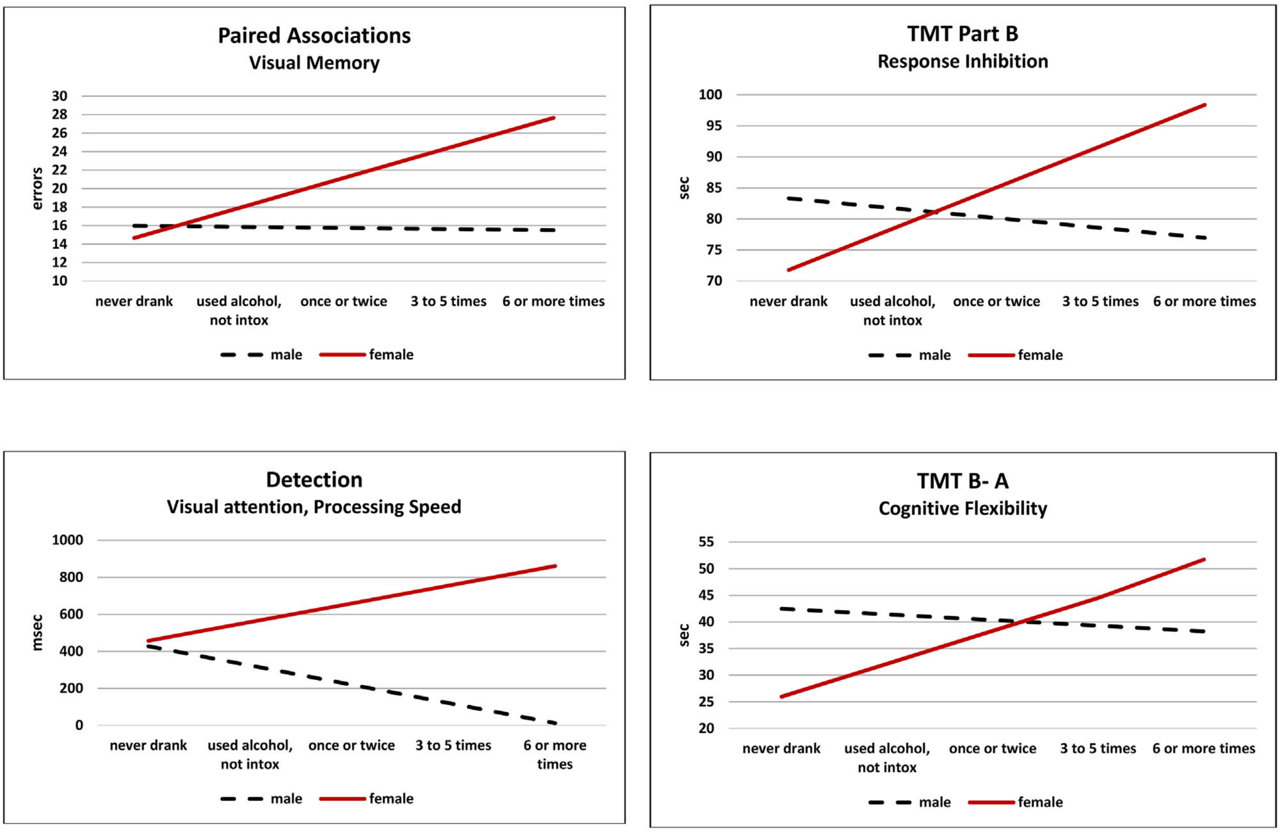

Figure 1. Interaction effects of sex by frequency of intoxication at adolescence (x-axis) on neurocognitive scores at age 21. Longer times (indicated by seconds or milliseconds) reflect poorer performance. TMT = Trail Making Test. msec = milliseconds. sec = seconds. Scores are adjusted for covariates.

consistent with our finding that males who engaged in frequent intoxication had better visual attention and speed of processing, as processing speed is highly dependent on visual-motor integration ability (Miyake et al., 2000). Thus, sex-specific brain activation in response to alcohol may offer one explanation of sex-divergent effects (Squeglia et al., 2014).

Other research indicates that adolescent binge drinking is associated with male-female differences in brain morphometry, with female drinkers exhibiting greater cortical thickness (less mature cortices), while male drinkers have thinner cortices (Squeglia et al., 2012, 2014). Thicker brain cortices would correspond to poorer visuospatial memory and inhibition, effects found in the current study among females with frequent past-year intoxication. Thus, the current findings coincide with several neuroimaging studies that show sex-specific neurological and morphological responses to alcohol, with females more susceptible to alcohol-related impairment (Jones et al., 2018; Medina et al., 2008; Spear et al., 2018; Tapert & Eberson-Shumate, 2022). However, the current study was not designed to investigate neurobiological mechanisms, thus the etiology of the sex differences found here is speculative.

The relative absence of alcohol effects in males is noteworthy, particularly given that males reported more frequent past-year intoxication than females. It has been suggested that males may be more resilient to the deleterious effects of heavy alcohol use, possibly recruiting compensatory cognitive systems to meet specific neurocognitive task demands (Squeglia et al., 2011). Male-female differences in body weight, alcohol metabolism, neuromaturation, and hormonal differences also might play a role (Squeglia et al., 2014). Girls' earlier pubertal development, which coincides with earlier prefrontal synaptic pruning, may place adolescent girls at a more neuromaturationally vulnerable stage than boys, as heavy alcohol use may inhibit healthy pruning (Medina et al., 2008). Future longitudinal neuroimaging studies involving males and females matched for brain development at baseline would be useful for better understanding the effect of alcohol on male-female brain structures and functions.

Although frequency of intoxication and binge drinking were positively correlated, only frequency of intoxication was associated with neurocognitive outcomes. Given that intoxication is affected by body weight, calorie intake at the time of drinking, and a host of additional factors, intoxication may be a more sensitive indicator of alcohol toxicity than binge drinking. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) (2021) definition of binge drinking involves number of drinks within a 2-hour period, but it does not account for differences in alcohol content. Thus, depending on the alcohol content per drink, it is possible that youth 'feel drunk' prior to the NIAAA definition of bingeing. It is also possible that intoxication reflects a higher blood alcohol concentration than that achieved by binge drinking standards and, therefore, would understandably link with more adverse neurocognitive outcomes (Tapert et al., 2004). More girls in the current sample reported past-year intoxication (32%) than past-month bingeing (18%), which likely strengthened the former's associations with neurocognition. Additionally, number of times intoxicated may be easier to remember and therefore more reliable than recall of number of occasions one drank a specific number of drinks. Subjective sense of intoxication has rarely been studied among adolescents vis-à-vis neurocognition (exceptions: Day et al., 2013; Jacob & Wang, 2020), yet current findings are particularly relevant as close to 20% of U.S. adolescents report past-year intoxication and 10% report past-month intoxication (Miech et al., 2020). In the current sample, teens who drank in the past year reported being intoxicated an average of 3 to 5 times.

Limitations of the current study should be considered in evaluating its findings. It is possible that deficits in neurocognitive functioning preceded and influenced alcohol use at adolescence (Jones et al., 2018; Wetherill et al., 2013). Alcohol use was self-reported, with the past 12-month time frame for frequency of intoxication possibly inaccurate due to poor recall. In contrast, the relatively shorter 30-day time frame for frequency of binge drinking may not capture longstanding bingeing patterns, which have shown to be important for neuro-psychological functioning (Carbia et al., 2017a; Mota et al., 2013). While the current study controlled for use of other substances (cigarettes, marijuana) at both adolescence and young adulthood, this method is limited given the high collinearity between alcohol and other drug use as well as potential interactive effects. Finally, other potentially relevant factors, such as history of drinking since first use and extent of drinking between the adolescent and young adult study time points were not assessed.

Study strengths include tests of effects extending across a 5-year period within a moderately large sample, analysis of moderation by sex, and control of several relevant covariates. Illicit substance users at both adolescence and young adulthood were excluded, thereby reducing effects associated with illicit substance use. Additionally, inclusion of a working-class sample of Chilean adolescents from a cultural context of early and acceptable drinking increases representativeness in the field, which has largely involved university students (Carbia et al., 2018).

Directions for further research have been outlined in numerous sources (Carbia et al., 2018; Lees et al., 2019, 2020; Tapert & Eberson-Shumate, 2022). Consistent across such reviews is the need to more precisely quantify alcohol effects at various points in development. Given that real-life alcohol use patterns involve variation in age at onset, spurts of consistent and discontinued use, and age-related trends in excessive intake, it is important to consider all such factors in determining effects on cognition (Masten et al., 2009). In addition, there is a need to examine alcohol's unique impact on cognition and brain structure in males and females with sufficiently powered studies to clarify the differential sex effects reported in the literature (Alfonso-Loeches et al., 2013; Squeglia et al., 2009, 2011, 2012).

Conclusions

Findings from the current study suggest several adverse neurocognitive effects associated with frequent intoxication during adolescence for females. Neurocognitive screening of those with a history of excessive alcohol intake during adolescence might prove useful. Current findings as well as those in the literature could be incorporated into public service announcements aimed at dissuading excessive alcohol use in teenage girls. Analysis of public service messaging shows that providing evidence of alcohol-attributable long-term ill health and harm is most effective at reducing alcohol misuse in teenagers (Young et al., 2018).

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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