Long-term alcohol use in adolescence and neurocognition: a preliminary study

Outi Kaarre, Noora Heikkinen, Milja Vanninen, Tommi Tolmunen, Marja Äikiä, Tuomo Hänninen, Petri Kivimäki, Eila Laukkanen

Abstract

Background: Despite a large body of evidence of the negative effects of alcohol on cognitive functioning in adults, its effects in adolescence are still unclear. In previous studies, binge drinking in adolescence has been associated with poorer neurocognitive performance with regards attention, working memory, spatial functioning, verbal and visual memory and executive functioning. The aim of this study was to evaluate whether approximately 10 years of alcohol use from adolescence into early adulthood affects cognitive functioning. The participants were 39 subjects with heavy alcohol use measured at three time points over ten years using a shortened version of the Alcohol Use Disorders Identification Test (AUDIT-C) and 32 age-, gender- and education-matched controls.

Methods: The participants underwent neuropsychological assessment consisting of measures of intellectual ability, executive functions, and verbal and working memory. In addition, all participants were interviewed using a semi-structured diagnostic psychiatric interview (SCID). Participants were asked about their alcohol use in the previous 12 months using the AUDIT-C at three time points in ten years. Lifetime drug use was also recorded with a questionnaire.

Results: No statistically significant differences were found in any particular field of the neuropsychological evaluations.

Conclusions: In our study on healthy young adults, no significant differences were found in neuropsychological test results between alcohol users and non-users. Longitudinal studies are warranted to disentangle pre-existing defects from the dose-dependent effects of alcohol on neurodevelopment and to differentiate causes from consequences.

Introduction

The first reports of harmful effects of alcohol on cognitive functioning were published as early as the 1880s by Wernicke and Korsakoff. The relationship between chronic exposure to alcohol and cognitive impairment is well established in adults. These changes in cognition appear to recover to some extent during long-term abstinence (1). However, the effects of alcohol abuse on the young developing brain are far less known. Adolescence, the transition from childhood to adulthood, is a unique period of physical and psychological development. In adolescence, the brain and cognition undergo parallel development and domains such as social skills, executive functioning and attention develop. These domains are known to deteriorate in chronic alcohol abuse (2).

Brain maturation is not typically complete until an age of up to 25 years. The limbic system develops before the maturation of the prefrontal cortex, which results in an increased propensity for risky, impulsive behaviours and vulnerability to alcohol and other substances (3-5). Thus, the prefrontal cortex may be more vulnerable to the effects of alcohol than other brain regions (6). It has been hypothesized that heavy drinking may affect cognitive functions that rely on the medial temporal lobe and dorsolateral prefrontal cortex (7).

Based on the current literature, it appears that binge drinking during adolescence has a subtle but significant deleterious effect on neurocognitive functioning, e.g. on memory, attention, spatial skills, and executive functioning (8). For further details on the literature from the past 10 years see Table 1, in which the results of five cross-sectional and four longitudinal studies are presented.

Adolescents engaged in binge drinking, and those with more withdrawal and hangover symptoms, tend to show the greatest deviations in cognitive functioning. It has been hypothesized that post-drinking withdrawal and hangover symptoms may be even more detrimental than the quantity of alcohol consumed. (9). More severe hangover symptoms have been associated with worsened attention and visuospatial functioning (10, 11), as well as poorer performance in measures of immediate and delayed recall (12). Adolescents with alcohol use disorders or binge drinking show not only poorer neurocognitive performance, but also alterations in the grey and white matter brain structure and discrepant functional brain activation patterns (9).

A family history of alcoholism is related to cognitive disadvantages that may leave youths more vulnerable to the neurotoxic effects of alcohol use (9). Differences in neuromaturation and neural response patterns may cause an increased risk for the development of an alcohol use disorder or increased substance use severity (13, 14). Pre-existing differences in adolescents with a family history of alcoholism have been found in several studies even before the onset of drinking (9). A decreased inhibitory response in frontal brain regions during an inhibition task has been observed in 12-to 14-year-old adolescents with a family history of alcoholism before they initiated drinking (15). Differences in brain activation patterns in fMRI BOLD (blood oxygen level dependent) responses have also been reported, with lower activation before initiating alcohol use, and an increased response after binge drinking started (9).

The altered neurocognitive functioning of alcohol-using adolescents may be a symptom of a larger premorbid dysfunction of the prefrontal cortex, predisposing these adolescents to risky substance abuse (6). The neurocognitive deficits may lead to direct and indirect changes in neuromaturation, with effects that would extend into adulthood (9). Longitudinal investigations have disentangled premorbid factors from the consequences of heavy alcohol use. Even with pre-existing differences, a link between alcohol use and poorer neurocognitive functioning has been reported (9).

In this study, we examined the effects of approximately 10 years of heavy alcohol use from adolescence into early adulthood on cognitive functioning.

Table 1: Review of the literature: the effects of alcohol use on neurocognition in adolescents (2, 7, 16-23).

Study	Domains	Results	Conclusions
Mota et al. 2013 (7) 2-year follow-up 89 university students, 40 Non-BD, 16 Ex-BD (BD at initial, not at follow-up), 33 BD	Working memory, episodic memory and executive abilities	BD subjects performed less well in the WMS-III Logical Memory Subtest and committed more perseverative errors in the SOPT	Persistent binge drinking is associated with verbal memory and monitoring difficulties
Squeglia et al. 2009 (16) 3-year follow-up, baseline studies prior to initiating drinking 76 adolescents, 12-14 yrs. Adolescents who transitioned into heavy (n=25) or moderate (n=11) drinking versus non-drinkers	Neuropsychological test battery incl. visuospatial processing, speeded information processing, sustained attention, executive functioning, working memory, intellectual capacity, learning	Girls: more drinking days in the past year predicted a greater reduction in performance in visuospatial tasks. Boys: more hangover symptoms predicted a relative worsening of sustained attention	Initiating moderately heavy alcohol use and incurring hangover during adolescence may adversely influence neurocognitive functioning
Hanson et al. 2011 (17) 10-year follow-up 213 adolescents, 13-18 yrs, with (n=151) or without (n=62) alcohol and other substance use disorder See also Hanson et al. 2011b (18)	Neuropsychological assessment at baseline and semi-annually up to 10 years, incl. measures of intellectual ability, visuospatial organization, memory, executive functioning	Neuropsychological trajectories were significantly related to substance involvement patterns on verbal learning and memory, visuospatial memory and verbal attention/working memory. Heavier use patterns generally followed by poorer cognition. Heavy use was independently associated with poorer verbal memory over time	Alcohol and other drug use during adolescence and young adulthood may primarily influence performance that relies on later-maturing brain systems. Higher levels of withdrawal symptoms may signify greater neuropsychological impairment
Winward et al. 2014 (19) 4-week follow-up study 65 adolescents, 16-18 yrs, with histories of heavy episodic drinking (HED, n=39) versus 26 controls. Marijuana users were also investigated (see the original study for further information)	Neuropsychological recovery during abstinence; 3 test batteries with 2-week intervals during 4-week monitored abstinence	HED teens performed worse on prospective memory, cognitive switching, inhibition task accuracy, verbal memory, visuospatial construction and language and achievement. Improvements during abstinence were detected but not to the levels of controls	Alcohol-related influences on several underlying brain systems may predate the onset of alcohol abuse or dependence or take longer than four weeks to recover
Johnson et al. 2008 (20) Cross-sectional study 207 10th grade adolescents in China	Affective decision-making tests: two versions of the IGT and working memory test SOPT	BD adolescents showed significantly lower net scores in the original version of the IGT. IGT significantly predicted binge drinking	Affective decision making deficits, linked to a dysfunctional ventromedial prefrontal cortex in BD adolescents. Near-sightedness for future consequences linked to hypersensitivity to reward is a key characteristic of BD adolescents

Study	Domains	Results	Conclusions
Heffernan et al. 2010 (21) Cross-sectional study 50 adolescents, 17-19 y, 21 BD (14 females), 29 non-BD (24 females)	Prospective memory (PM); PRMQ and PRVP	No significant differences between either the self-reported long-term or short-term PM lapses. BD adolescents recalled significantly fewer location-action combinations in the PRVP	Binge drinking in the teenage years leads to impairments in everyday PM
Ferret et al 2010 (22) Cross-sectional study 52 South African adolescents 13-15 y, AD n=26, controls n=26	A general-purpose neuropsychological test battery incl. verbal story memory, verbal list learning, self-monitoring and regulation, planning and problem solving, psychomotor speed and coordination, attention and concentration, sequencing ability, expressive language, visuospatial construction and visual memory	Adolescents with AD performed worse in measures of Verbal Story Memory, Self-Monitoring and Psychomotor Speed and Coordination	Adolescents with AD may be at increased risk for failure to reach optimal levels of neuromaturation, and may be susceptible to cognitive problems associated with protracted alcohol consumption
Thoma et al. 2011 (2) Cross-sectional study 48 adolescents (12-18 y) in 3 groups: controls (n=15), alcohol/marijuana abusers/dependents (SUD, n=19), and those with a family history of alcoholism but no personal abuse (FHP; n=14)	6 neuropsychological composites: Verbal Reasoning, Visuospatial Ability, Executive Function, Memory, Attention & Processing Speed	More drinks per day predicted poorer performance for attention and executive function composites. SUD group had lower scores for attention, memory and processing speed composites. Poorer visuospatial ability in the FHP group	Heavy alcohol use leads to a reduction in attention and executive functioning. A family history of alcoholism is associated with deficits in visuospatial ability
Parada et al. 2012 (23) Cross-sectional study 122 undergraduates, 18-20 y, 62 BD (30 females) versus 60 non-BD (29 females)	Executive functions; WMS-III Backward Digit Span & Backward Spatial Span, SOPT (abstract designs), Letter Fluency (PMR), BADS (Zoo Map and Key Search) and WCST-3	BD students scored lower in the Backward Digit Span Subtest and generated more perseverative responses in the SOPT. In relation to the interaction BD by sex, BD males scored lower in the Backward Digit Span test than BD females and non-BD males	BD is associated with poorer performance in executive functions subserved by the dorsolateral prefrontal cortex. These difficulties may reflect developmental delay or frontal lobe dysfunction

Abbreviations: AD = alcohol dependence; BADS = Behavioural Assessment of Dysexecutive Syndrome; BD = binge drinkers; Ex-BD = binge drinker at initial, not at follow-up; IGT = Iowa Gambling Test; PRMQ = Prospective and Retrospective Memory Questionnaire; PRVP = Prospective Remembering Video Procedure; SOPT = Self-Ordered Pointing Task; WCST-3 = Wisconsin Card Sorting Test-3; WMS-III = Wechsler Memory Scale-III; HED = heavy episodic drinking; PM = prospective memory

Material and methods

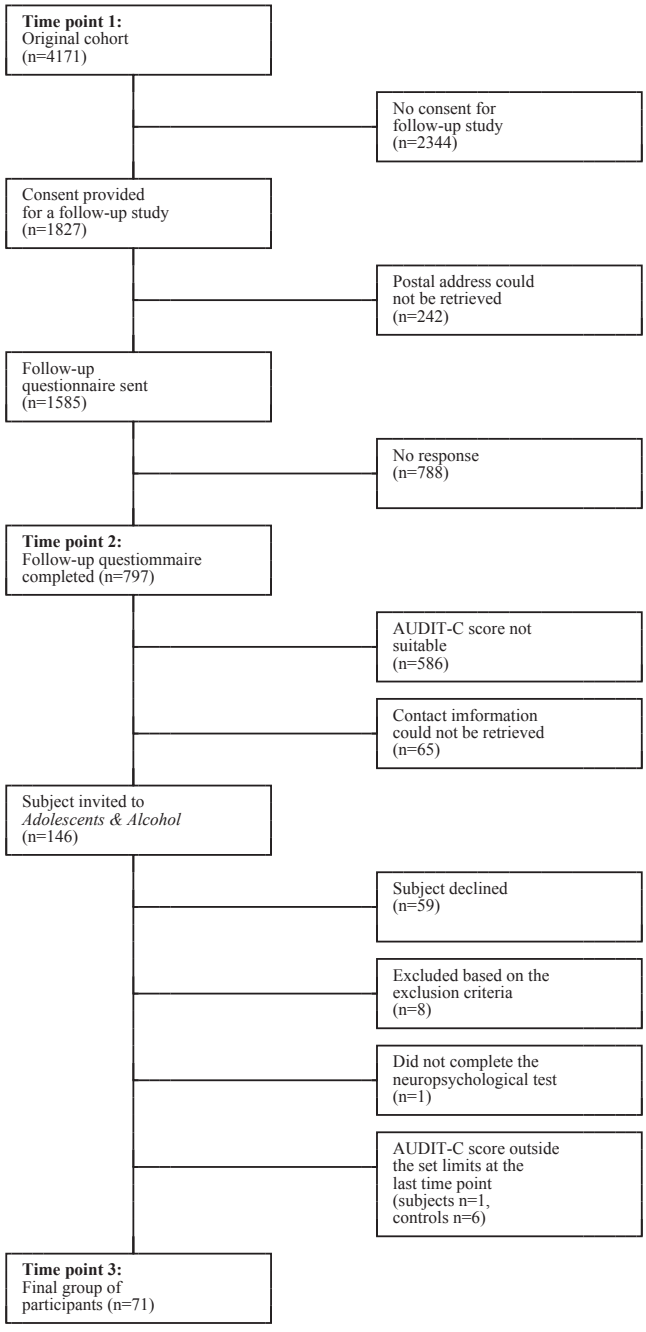
Subjects

This study formed a part of the ongoing Adolescents and Alcohol project, which is recording the health and alcohol use of Finnish adolescents. The aim of the project is to provide information on the maturation of the adolescent brain under the influence of long-term alcohol use. In particular, the brain structure and neurophysiological functioning, as well as the cognitive, psychosocial, and psychological functioning of the participants, are being targeted. Permission for the study was provided by the Kuopio University Hospital Research Ethical Committee, the Finnish National Supervisory Authority for Welfare and Health, and the Finnish Ministry of Social Affairs and Health.

The baseline and follow-up study settings have been previously described (24, 25). The participants of the original cohorts (years of birth 1986-1991), gathered in 2004-2005, were attending school in Kuopio, a city in Eastern Finland with approximately 90,000 inhabitants, including 7087 13-to 18-year-old adolescents at the time. The parents of 666 adolescents refused the participation of their children, and the final response rate was 65.5% (n=4214). Adolescents attending special needs education were excluded. All participants took the Alcohol Use Disorders Identification Test (AUDIT) and completed a questionnaire concerning their substance use, mental health and lifestyle (time point 1). A similar follow-up questionnaire was sent in 2010-2011 by mail to those who had provided consent to be contacted for a follow-up study and whose postal address could be retrieved (n=1585).

Participants were asked about their alcohol use in the previous 12 months using the AUDIT, which is a structured questionnaire originally designed by the World Health Organization. In this study, we used a shortened version of the AUDIT, AUDIT-C (items 1-3; range 0-12), which is composed of only the first three questions concerning the level of alcohol consumption during the previous year ("How often do you have a drink containing alcohol?", "How many drinks containing alcohol do you have on a typical day when you are drinking?" and "How often do you have six or more drinks on one occasion?"). Lifetime drug use was also recorded using a questionnaire in which the participants were asked to report whether they had tried different drugs (as named in the questionnaire according to category) never, 1-5 times or more than six times. Additionally, past and present cigarette smoking were recorded. Participants for the present study were selected from those who completed the follow-up questionnaire (n=797, time point 2). The selection of the participants is illustrated in Figure 1.

Figure 1. Selection of the participants.



A participant was defined as a subject if the AUDIT-C score was 3 or more at time points 1 and 2. Subjects were organized as a list in descending order based on two criteria: AUDIT-C scores at time point 2 and at time point 1. Subjects were contacted in this descending order, and age-, gender- and education-matched controls were recruited one by one as the alcohol-using subjects participated in the study. The controls had the lowest AUDIT-C scores (maximum 2) at both time points. Other participants were classified as not suitable. The exclusion criteria were substantial head injury needing medical treatment, neurological illness, metal or implanted devices in the body contraindicating MRI, the use of other intoxicating substances and pregnancy. A research assistant contacted potential participants by telephone, e-mail and letter. Sixty-five subjects could not be contacted because of missing contact information.

In total, 146 participants were contacted, of whom 59 declined to participate, 7 were excluded based on the exclusion criteria, and one participant did not perform the neuropsychological test due to scheduling problems. One participant was excluded due to binge drinking episodes but no regular alcohol use. One alcohol-using participant was excluded due to an AUDIT-C score of less than three, and six abstinent control participants were excluded due to an AUDIT-C score of more than two at the last time point. Prior to participating in the study, written consent was requested from all participants.

Methods

At the final time point, i.e. time point 3, the participants took part in neuropsychological evaluations and psychiatric interviews. All participants were interviewed using a semi-structured diagnostic psychiatric interview (SCID, 26). Interviews were conducted by specialists in adolescent psychiatry trained for SCID interviews. Participants were asked about their alcohol use during the previous 12 months using the AUDIT-C, and lifetime drug use was also recorded with a questionnaire.

Neuropsychological assessment

Neuropsychological assessment consisted of measures of intellectual ability and working memory, as well as verbal learning and memory and executive functions. The neuropsychological tests are presented in Table 2.

Table 2. Neuropsychological tests used in the study (27-29).

Cognitive domain	Functions	Test	Used subtests
Intellectual ability	* Verbal ability * Perceptual Reasoning	Wechsler Adult Intelligence Scale III *(WAIS III)*	* Similarities (S) * Matrix Reasoning (MR)
Executive functions	* Processing speed and mental flexibility	Trail Making Test *(TMT)*	* TMT A * TMT B
	* Processing speed and mental flexibility * Selective attention	Stroop Test	
	* Psychomotor performance * Processing speed	Wechsler Adult Intelligence Scale III	* Digit symbol (DSy)
	* Verbal fluency		* Phonemic fluency (PAS)
	* Auditory information processing speed * Calculation ability	Paced Auditory Serial Addition Test *(PASAT)*	
Working memory	* Attention span * Verbal working memory	Wechsler Adult Intelligence Scale III	* Digit Span (DSp) * Letter-Number Sequencing (LNS)
Memory	* Verbal memory * Delayed memory	Wechsler Memory Scale - Revised (WMS-R)	* Story Recall
	* Verbal learning and memory	Word List Learning test	

Verbal learning and memory were evaluated with the Word List Learning Test, in which the scores were the sum of the words recalled over the four learning trials, and the percentage retention score of the learned words was the measure for delayed recall. In Story Recall, the scores were the number of story units recalled immediately, and the percentage retention score of the story content was calculated for delayed memory. Executive functions were evaluated with the Trail Making Test and the Stroop Test. Difference scores of time (in the Trail Making Test, B - A; in the Stroop Test, C: interference - B: colour naming) were used as measures for processing speed.

WAIS III Similarities and Matrix Reasoning were used as measures for verbal and perceptual intellectual ability. Raw scores were used in statistical analysis. In Digit Span and Letter-Number Sequencing, which are measures of working memory, the sum scores of correct responses were used. In the Digit Symbol task, used to evaluate psychomotor performance, the variable was the number of correctly drawn items. In PASAT, measuring the auditory information processing speed, the number of correct responses was used, and in Phonemic Verbal Fluency task, the sum of words correctly named with given letters was calculated.

For neuropsychological tests, structured instructions were used according to test manuals and established clinical practice. Assessments were conducted in the morning by experienced psychologists trained in the use of the test battery. The psychologists did not know whether the participant was a subject or a control.

Statistics

The data were considered normally distributed when the skewness and kurtosis were between -1 and +1. Chi-squared tests were run to compare groups based on demographic variables including gender, educational background, and the prevalence of smoking, marijuana and other drug use. The difference in mean ages between groups at different time points was tested with a 2-tailed independent samples t-test, and the difference in mean AUDIT-C scores with the Mann-Whitney U-test. The results of the neuropsychological tests, apart from the Stroop Process data, were analysed using the independent samples t-test. The Mann-Whitney U-test was used for analyzing the Stroop Process data. Due to multiple testing, Bonferroni correction was used to determine the significance level. The level of significance was thus set to 0.004 (0.05 divided by 13). The statistical analyses were carried out using IBM SPSS Statistics, version 21.

Results

The demographic characteristics of the participants are presented in Table 3, and the AUDIT-C scores of control participants at different time points are listed in Table 4.

There were no statistically significant differences between the groups in the use of drugs. The mean AUDIT-C scores of male subjects versus female subjects and male controls versus female controls were also compared. They did not differ significantly at any time point. Smoking was significantly more common among alcohol-using adolescents.

Fifteen subjects and twelve controls had a lifetime DSM-IV psychiatric diagnosis according to the SCID interview. Six subjects and four controls had more than one psychiatric diagnosis. No current major depression was diagnosed in any of the participants. There was no statistically significant difference in the prevalence of current psychiatric diagnoses between the two groups ($p>0.05$). The diagnoses are presented in Table 5.

There were no statistically significant differences in neuropsychological evaluation. The neuropsychological test results are presented in Table 6.

Table 3. Demographic characteristics of the participants.

	Subjects n=39	**Controls n=32**	**P value**
Male/Female	18/21	15/17	ns
Age, mean ±SD			
Time point 1	16.1 ± 1.2	15.5 ± 1.5	ns
Time point 2	22.1 ± 1.2	21.6 ± 1.5	ns
Time point 3	24.8 ± 1.4	24.6 ± 1.7	ns
Audit-C			
Time point 1	6.1 ± 1.8	0.06 ± 0.4	<0.001
Time point 2	8.3 ± 0.9	0.3 ± 0.5	<0.001
Time point 3	6.5 ± 2.1	0.8 ± 0.8	<0.001
Smoking %	46.2	6.3	<0.001
Lifetime cannabis use %*	7.7	0	ns
Lifetime other drug use %*	0	0	ns
Education			
Comprehensive school	0	1	ns
Secondary school	21	9	ns
University/polytechnic	18	22	ns

*Reported use of more than 6 times during lifetime.
Abbreviation: ns = non-significant, $p > 0.05$.

Table 4. AUDIT-C scores of control participants at the different time points.

Time point	AUDIT-C score		
	0	1	2
1 (2005)	31		1
2 (2010)	23	8	1
3 (2015)	13	11	8

Table 5. Number of different lifetime psychiatric diagnoses of the participants.

DSM-V Diagnosis	Subjects		Controls	
	Current	Past	Current	Past
Anxiety disorders	3	3	4	3
Mood disorders	0	5	1	5
Personality disorders	4	0	3	0
Eating disorder	0	1	0	1
Alcohol use disorder	1	1	0	0

Table 6. Results of neuropsychological test battery.

Cognitive domain	Subjects mean ± SD	Controls mean ± SD	P value
Intellectual ability			
WAIS III Similarities	23.49 ± 3.66	24.47 ± 3.60	0.261
Matrix Reasoning	21.59 ± 2.29	20.69 ± 2.83	0.142
Executive functions and attention			
Trail Making process (sec)	33.90 ± 15.73	41.38 ± 21.81	0.098
Stroop test process (sec)	median 30.0 (26.00-39.50)	median 40.50 (31.50-49.50)	0.017
WAIS III Digit symbol	82.21 ± 14.55	82.03 ± 13.43	0.959
PASAT sum	47.67 ± 9.39	48.27 ± 9.60	0.795
Verbal fluency			
Phonemic fluency, sum	47.59 ± 12.30	47.25 ± 15.25	0.918
Working memory			
WAIS III Digit Span	16.44 ± 3.19	15.97 ± 3.80	0.576
Letter-Number Sequencing	11.64 ± 2.03	11.88 ± 2.85	0.688
Memory			
Story Recall; immediate	13.08 ± 4.11	14.19 ± 4.37	0.274
Delayed	12.13 ± 3.98	12.81 ± 4.42	0.495
Word List Learning test, sum	41.77 ± 5.50	42.22 ± 6.96	0.762
Word List Learning test, percent retention	86.45 ± 15.78	85.69 ± 17.65	0.855

Discussion

Summary of the main findings

In this preliminary study, we examined cognitive functioning in healthy adolescents with a long-term history of alcohol use and in age-, gender- and education-matched controls. No statistically significant differences were found in any particular field of neuropsychological evaluations.

Comparisons with existing literature

In previous studies, subtle changes have been reported in attention and information processing, memory, visuospatial functioning, language abilities and executive functioning in alcohol-using adolescents (8, 9, 30). Some previous studies have only included adolescents with alcohol use disorder, while others have also included binge drinkers. Although there are links between binge drinking and alcohol use disorders, in the context of neuropsychological evaluations, it is important to distinguish between them (30). In some previous studies, the alcohol use of the study subjects has been defined in various ways. For example, the consumption of six or more alcohol portions on the same occasion has been used as a measure of binge drinking (7), while in other studies, various questionnaires such as the Customary Drinking and Drug Use Record (CDDR) have been applied (17). These differences in defining the use of alcohol make the comparison of results more difficult.

This may explain why no neuropsychological differences were found in our study: the alcohol use of our study subjects might have been less profuse than in some previous studies. Our study subjects had mean AUDIT-C scores above 6 at all 3 time points (see Table 3). Thus, they had consumed large amounts of alcohol for approximately ten years. However, only one of the subjects met the diagnostic criteria for previous alcohol use disorder.

Psychiatric comorbidities are common in patients with substance use disorders. For example, individuals with excessive alcohol use have increased depressive symptoms, and depressed patients are more likely to abuse alcohol (6). Little is known about the combined impact of depression and alcohol use disorder on the developing brain (30). In one study, binge drinkers with primary depression performed consistently worse than

controls or those with either depression or binge drinking; visual learning and memory were significantly impaired (31). Furthermore, depression itself may cause cognitive dysfunction in adolescents (32). In our study, depression was the most common psychiatric diagnosis among the participants, but there were no differences in the prevalence of depression between the groups.

Strengths and limitations

The strength of this study is that alcohol use was evaluated with a commonly applied and validated method and that the psychiatric interviews were conducted by experienced specialists. Cognitive function was evaluated with a comprehensive test battery. The limitation of this investigation is that no baseline data on the neuropsychological functioning of the study subjects was available. Thus, the pre-existing differences between groups in cognitive functioning could not be evaluated. However, all study participants had completed their basic education at comprehensive school, indicating that they did not have major learning disabilities. All but one participant had continued studying after comprehensive school. Based on the participants' educational background, it could be assumed that on average they had relatively good cognitive skills at baseline.

AUDIT records the alcohol use of a participant during the previous twelve months. Thus, the volume and pattern of alcohol use were known for three out of the ten years of the study. There is a possibility that the alcohol use of the study subjects deviated from the set limits during these periods. However, the general developmental course of alcohol use has previously been shown to be well established: drinking usually accelerates during adolescence, peaks during young adulthood, and then decreases to more moderate use. Adolescent binge drinking trajectories have previously been investigated. The most common trajectories, according to Tucker et al. (33), were non-binge drinking (approximately one-third) and moderate stable binge drinking (not exceeding one episode of binge drinking during the previous month; approximately one-third). Thus, it can be assumed that the drinking habits of our study subjects had been relatively stable.

Three subjects in our study had used cannabis more than six times during their lifetime. One reported using cannabis 10 times in the past, another reported using it once a week for a year, amounting to approximately 52 times several years previously, and the third remembered using it "more than ten times". Previous studies have suggested that the use of alcohol alone may be more detrimental than the combined use of alcohol and marijuana (18). Since cannabis use was rather common in our sample, it

could be speculated whether this affected the results. However, no cannabis use disorders were diagnosed, and it is likely that the small amount of reported cannabis use in our sample was mostly occasional and did not therefore affect cognitive functioning. Additional research is needed to determine the effects of heavy alcohol use versus combined alcohol and other drug use on neurocognition.

Implications for future research

The direction of causality in the association between alcohol abuse and neurocognitive defects in adolescents is still partly unclear. In other words, the extent to which the neurobiological and structural changes found in previous studies were pre-existing versus alcohol-induced, and whether some of these changes may even cause alcohol abuse, is not known. It has also remained unclear why problem drinking influences some adolescents more than others, and precisely which neurobiological pathways are affected by alcohol use during normal brain development (30). It is additionally important to determine whether and when the critical periods of heightened vulnerability to the effects of alcohol occur (8), and whether there are protective and predisposing factors. Since the underlying mechanisms causing cognitive deficiencies are not well known, future work should focus on uncovering these mechanisms and disentangling pre-existing differences from the dose-dependent effects of alcohol on neurodevelopment.

References

1. Fein G, Torres J, Price LJ, Di Sclafani V. Cognitive Performance in Long-Term Abstinent Alcoholics. Alcoholism, clinical and experimental research. 2006;30(9):1538-1544.

2. Thoma RJ, Monnig MA, Lysne PA, et al. Adolescent Substance Abuse: The Effects of Alcohol and Marijuana on Neuropsychological Performance. Alcoholism, clinical and experimental research. 2011;35(1):39-46.

3. Arain M, Haque M, Johal L, Mathur P, Nel W, Rais A, Sandhu R, Sharma S. Maturation of the adolescent brain. Neuropsychiatric Disease and Treatment 2013 9:449-461.

4. Bava S, Tapert SF. Adolescent brain development and the risk for alcohol and other drug problems. Neuropsychol Rev 2010;20(4):398-413.

5. Hermens DF, Lagopoulos J, Tobias-Webb J, De Regt T, Dore G, Juckes L, Latt N, Hickie IB. Pathways to alcohol-induced brain impairment in young people: a review. Cortex. 2013 Jan;49(1):3-17.

6. De Bellis MD, Narasimhan A, Thatcher DL, Keshavan MS, Soloff P, Clark DB. Prefrontal Cortex, Thalamus, and Cerebellar Volumes in Adolescents and Young Adults with Adolescent-Onset Alcohol Use Disorders and Comorbid Mental Disorders. Alcohol Clin Exp Res 2005;29:1590-1600.

7. Mota N, Parada M, Crego A, Doallo S, Caamano-Isorna F, Rodriguez Holgu¡n S, Cadaveira F, Corral M. Binge drinking trajectory and neuropsychological functioning among university students: a longitudinal study. Drug Alcohol Depend. 2013 Nov 1;133(1):108-114.

8. Squeglia LM, Jacobus J, Tapert SF. The Influence of Substance Use on Adolescent Brain Development. Clinical EEG and neuroscience: official journal of the EEG and Clinical Neuroscience Society (ENCS). 2009;40(1):31-38.

9. Squeglia LM, Jacobus J, Tapert SF. The effect of alcohol use on human adolescent brain structures and systems. Handbook of clinical neurology. 2014;125:501-510.

10. Tapert SF, Granholm E, Leedy NG, Brown SA. Substance use and withdrawal: neuropsychological functioning over 8 years in youth. J Int Neuropsychol Soc. 2002 Nov; 8(7):873-883.

11. Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF. Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. Psychol Addict Behav. 2009 Dec; 23(4):715-722.

12. Mahmood OM, Jacobus J, Bava S, Scarlett A, Tapert SF. Learning and memory performances in adolescent users of alcohol and marijuana: interactive effects. J Stud Alcohol Drugs. 2010 Nov; 71(6):885-894.

13. Jacobus J, Tapert SF. Neurotoxic effects of alcohol in adolescence. Annu Rev Clin Psychol 2013;9:703-721.

14. Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain Response to Working Memory Over Three Years of Adolescence: Influence of Initiating Heavy Drinking. Journal of Studies on Alcohol and Drugs. 2012;73(5):749-760.

15. Schweinsburg AD, Paulus MP, Barlett VC, Killeen LA, Caldwell LC, Pulido C, Brown SA, Tapert SF. An FMRI study of response inhibition in youths with a family history of alcoholism. Ann N Y Acad Sci. 2004 Jun; 1021():391-394.

16. Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF. Initiating Moderate to Heavy Alcohol Use Predicts Changes in Neuropsychological Functioning for Adolescent Girls and Boys. Psychology of addictive behaviors: journal of the Society of Psychologists in Addictive Behaviors. 2009;23(4):715-722.

17. Hanson KL, Cummins K, Tapert SF, Brown SA. Changes in Neuropsychological Functioning over 10 Years Following Adolescent Substance Abuse Treatment. Psychology of addictive behaviors: journal of the Society of Psychologists in Addictive Behaviors. 2011;25(1):127-142.

18. Hanson KL, Medina KL, Padula CB, Tapert SF, Brown SA. Impact of Adolescent Alcohol and Drug Use on Neuropsychological Functioning in Young Adulthood: 10-Year Outcomes. Journal of child & adolescent substance abuse. 2011;20(2):135-154.

19. Winward JL, Hanson KL, Bekman NM, Tapert SF, Brown SA. Adolescent Heavy Episodic Drinking: Neurocognitive Functioning during Early Abstinence. Journal of the International Neuropsychological Society: JINS. 2014;20(2):218-229.

20. Johnson CA, Xiao L, Palmer P, et al. Affective decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in 10th grade Chinese adolescent binge drinkers. Neuropsychologia. 2008;46(2):714-726.

21. Heffernan T, Clark R, Bartholomew J, Ling J, Stephens R. Does binge drinking in teenagers affect their everyday prospective memory? Drug Alcohol Depend. 2010 Jun 1;109(1-3):73-78.

22. Ferrett HL, Carey PD, Thomas KG, Tapert SF, Fein G. Neuropsychological performance of South African treatment-naive adolescents with alcohol dependence. Drug Alcohol Depend. 2010 Jul 1;110(1-2):8-14.

23. Parada M, Corral M, Mota N, Crego A, Rodriguez Holguin S, Cadaveira F. Executive functioning and alcohol binge drinking in university students. Addict Behav. 2012 Feb;37(2):167-172.

24. Laukkanen E, Rissanen M-L, Honkalampi K, Kylmä J, Tolmunen T, Hintikka J. The prevalence of self-cutting and other self-harm among 13- to 18-year-old Finnish adolescents. Soc Psychiatry Psychiatr Epidemiol 2009;44:23-28.

25. Kekkonen V, Kivimäki P, Valtonen H, Tolmunen T, Lehto SM, Hintikka J, Laukkanen E. Sample selection may bias the outcome of an adolescent mental health survey: results from a 5-year follow-up of 4171 adolescents. Public Health. 2015 Feb;129(2):162-172.

26. Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association 1994).

27. Latvala A, Castaneda AE, Peräjä J, Saarni SI, Aalto-Setälä T, Lönnqvist J, Kaprio J, Suvisaari J, Tuulio-Henriksson A. Cognitive functioning in substance abuse and dependence: a population- based study of young adults. Addiction. 2009 Sep;104(9):1558-1568.

28. Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment, Fourth Edition. New York: Oxford University Press, Inc. 2004.

29. Kanninen A, Hämälä M, Palomäki H. Neuropsykologian käsitteet - sanakirja neurokliinikoille. Helsinki: Helsingin Psykotutkimus Oy. 1997.

30. Hermens DF, Lagopoulos J, Tobias-Webb J, De Regt T, Dore G, Juckes L, Latt N, Hickie IB. Pathways to alcohol-induced brain impairment in young people: a review. Cortex. 2013 Jan;49(1):3-17.

31. Hermens DF, Lee RS, De Regt T, Lagopoulos J, Naismith SL, Scott EM, Hickie IB. Neuropsychological functioning is compromised in binge drinking young adults with depression. Psychiatry Res. 2013 Nov 30;210(1):256-262.

32. Basnet P, Noggle CA, Dean RS. Neurocognitive Problems in Children and Adolescents With Depression Using the CHC Theory and the WJ-III. Appl Neuropsychol Child. 2014 Nov 20:1-9.

33. Tucker JS, Orlando M, Ellickson PL. Patterns and correlates of binge drinking trajectories from early adolescence to young adulthood. Health Psychol. 2003 Jan;22(1):79-87.

Outi Kaarre, M.D.
Department of Adolescent Psychiatry, Kuopio University Hospital

Noora Heikkinen, M.Soc.Sc., B.M,
University of Eastern Finland

Milja Vanninen, B.M.
University of Eastern Finland

Tommi Tolmunen, M.D., Ph.D.
Department of Adolescent Psychiatry, Kuopio University Hospital and
School of Medicine, University of Eastern Finland

Marja Äikiä, Ph.D
Department of Neurology, Kuopio University Hospital

Tuomo Hänninen, Ph.D.
Department of Neurology, Kuopio University Hospital

Petri Kivimäki, B.M.
University of Eastern Finland

Eila Laukkanen, M.D., Ph.D., Professor
Department of Adolescent Psychiatry, Kuopio University Hospital and
School of Medicine, University of Eastern Finland

Correspondence:
outi.kaarre@kuh.fi