Received: 30 August 2022 | Accepted: 6 February 2023

DOI: 10.1111/acer.15037

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RESEARCH ARTICLE

The impact of age on olfactory alcohol cue-reactivity: A functional magnetic resonance imaging study in adolescent and adult male drinkers

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Funding information
H2020 European Research Council, Grant/Award Number: 947761

Abstract

Background: Adolescence is marked not only by rapid surges in the prevalence of alcohol use disorders (AUDs) but also by remarkable recovery rates, as most adolescent-onset AUDs naturally resolve over time. Little is known about the differential vulnerability of adolescents and adults. Therefore, this study aimed to unravel the moderating role of age by comparing neural alcohol cue-reactivity, an important AUD biomarker, between low-to-high beer-drinking adolescent (n = 50, 16 to 18 years), and adult (n = 51, 30 to 35 years) males matched on drinking severity.

Methods: Associations between beer odor-induced brain activity and AUD diagnosis, severity of alcohol use-related problems, recent alcohol use, binge-drinking frequency, and task-induced craving were investigated across and between age groups in regions of interest thought to be central in alcohol cue-reactivity: the medial prefrontal cortex, anterior cingulate cortex, and striatal subregions (nucleus accumbens and caudate putamen). These analyses were complemented by exploratory whole-brain analyses.

Results: Pre-task beer craving increased pre-to-post task in adolescents only. Individual differences in alcohol use, binge drinking, and craving did not relate to beer odor-induced activity. Although region-of-interest analyses did not reach significance, whole-brain analyses showed that adolescents with AUD, compared with adolescents without AUD and adults with AUD, had higher beer odor-induced activity in a large mesocorticolimbic cluster encompassing the right caudate, nucleus accumbens, orbitofrontal cortex, and the olfactory sulcus. Activity in the right caudate and putamen was positively associated with the severity of alcohol use-related problems in adolescents but negatively associated in adults.

Conclusion: These findings suggest a differential role of alcohol cue-reactivity in adolescents compared with adults with AUD and highlight the need for further studies investigating the role of age in the fundamental processes underlying the development of and recovery from of AUD.

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KEYWORDS
adolescence, age, alcohol, alcohol use disorder, fMRI, olfactory cue-reactivity

INTRODUCTION

Adolescence marks rapid increases in the prevalence of binge drinking and alcohol use disorders (AUDs; Chassin et al., 2004; Johnston et al., 2018; Lee et al., 2018). Previous work stresses the potential negative impact of alcohol use on the developing brain (for review, see Conrod & Nikolaou, 2016; De Goede et al., 2021; Lees et al., 2019) and the generally worse prognosis for early-onset AUD (Hingson et al., 2006). However, the higher recovery rates of adolescent-onset AUDs during young adulthood relative to older age groups (Chassin et al., 2004; Lee et al., 2018) suggest possible resilience. Little is known about the differential AUD vulnerability of adolescents versus adults. Therefore, this study aimed to unravel the moderating role of age by investigating the relation between neural alcohol cue-reactivity, an important AUD biomarker (Zeng et al., 2021), and the severity of alcohol use in adolescent compared with adult drinkers.

Alcohol use disorder is characterized by the inability to control alcohol use, despite significant negative consequences on daily life and health (APA, 2013). Over the course of alcohol use towards dependence, the salience of alcohol-related cues increases, which is thought to parallel the development of alcohol cue-induced hyperresponsivity of mesocorticolimbic brain areas involved in reward processing, attention, alcohol-seeking behavior and craving (Cofresí et al., 2019). A recent voxel-based meta-analysis showed consistent alcohol cue-reactivity in the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) in adults with AUD compared with adults without AUD (Zeng et al., 2021). Elevated alcohol cue-reactivity is also commonly observed in striatal areas and a shift from the involvement of ventral areas such as the nucleus accumbens (Nacc) to dorsal areas such as the caudate and putamen is thought to reflect a transition from reward-driven to habitual/compulsive alcohol use (Cofresí et al., 2019; Vollstädt-Klein et al., 2010). Although somewhat inconsistent across studies, elevated alcohol cue-reactivity in mesocorticolimbic areas has been related to different measures of AUD severity, craving and relapse and is therefore considered an important AUD biomarker (Cofresí et al., 2019; Zeng et al., 2021).

Developmentally normative increases in risk-taking, reward sensitivity, emotional sensitivity and social sensitivity, combined with more protracted development of behavioral control are thought to increase adolescents' risks to develop AUD (Conrod & Nikolaou, 2016; Cousijn et al., 2018). Relative to a control group, adolescents at-risk of addiction (based on their familial history or prospective data) consistently display heightened activity in the putamen during a variety of neuroimaging tasks that involve a reward/motivational component (Tervo-Clemmens et al., 2020). Longitudinal neuroimaging studies report evidence for dose-related accelerated reductions in prefrontal gray matter volume and preliminary evidence for parallel changes in brain functionality after the initiation of heavy drinking (De Goede et al., 2021). Binge drinking may be particularly harmful, showing a consistent association with inhibitory control deficits in adolescents and young adults (Carbia et al., 2018). Preliminary results from rodent studies comparing adolescent-onset and adult-onset drinkers suggest a complex role of age: adolescent-onset drinkers show higher sensitivity to the rewarding effects of alcohol, lower sensitivity to the intoxicating effects of alcohol, reduced dopaminergic transmission in the Nacc and PFC, more extensive neurodegeneration and impaired neurogenesis (for a systematic review see Kuhns et al., 2022). Interestingly, however, adolescent-onset drinkers may also better retain cognitive flexibility (Fernandez et al., 2017; Pickens et al., 2019) and regain control over alcohol-seeking after abstinence (Labots et al., 2018), highlighting potential resilience to AUD-like behavior.

To the best of our knowledge, only a handful of studies directly investigated the impact of age on the relation between alcohol use and (neuro)cognitive functioning in humans, including three behavioral studies (Cousijn et al., 2020; McAteer et al., 2018; Rooke & Hine, 2011) and one resting-state neuroimaging study (Müller-Oehring et al., 2018; for a systematic review, see Kuhns et al., 2022). Although the attentional bias towards alcohol cues (i.e., relative automatic attentional capture and maintenance) did not differ with age (Cousijn et al., 2020; McAteer et al., 2018), adolescents showed stronger implicit alcohol-memory associations that more strongly predicted binge drinking compared with adults (Rooke & Hine, 2011). In moderate compared with light 12- to 21-year-old drinkers, normative age-related increases in superior frontal gyrus to insula connectivity were absent and amygdala to medial parietal functional synchrony was reduced (Müller-Oehring et al., 2018). These preliminary findings highlight the need for further studies, including investigations of individuals with more severe levels of alcohol use. Moreover, current neurocognitive models of addiction are mainly based on adult data, and knowledge about the potential differences between adolescent and adult AUD may have important value for theory and clinical practice, stimulating further development of age-tailored intervention programs.

The goal of this explorative study was to investigate the moderating role of age in the relationship between neural alcohol cue-reactivity and severity of alcohol use. Brain activity in response to beer versus appetitive (juice) and neutral (water) control odors was measured in low-to-high drinking adolescent and adult males closely matched on current drinking severity. We included mid-to-late adolescents aged 16 to 18 and adults aged 30 to 35 to capture the normative periods during which alcohol use starts to escalate and deescalate (Britton et al., 2015; Windle, 2020). Beer and juice cravings were assessed before and after the task. To capture different

aspects of problematic alcohol use, the association between beer odor cue-reactivity and AUD diagnosis (YES/NO), severity of alcohol use-related problems (AUD identification test (Saunders et al., 1993)) quantity of recent alcohol use, frequency of binge drinking, and craving were investigated across and between age groups. We used a region of interest (ROI) approach, focusing on meta-analysis derived areas in which alcohol cue-reactivity differed between individuals with and without AUD (mPFC, dACC; Zeng et al., 2021) and striatal subregions that are hypothesized to mediate reward-driven versus habitual/compulsive alcohol use (Nacc, putamen, caudate; Cofresí et al., 2019; Vollstädt-Klein et al., 2010). Given the novelty of the age group comparison, ROI analyses are presented uncorrected and corrected for multiple comparisons. Moreover, ROI analyses were complemented with exploratory whole-brain multiple comparison corrected analyses. Based on human developmental literature (Conrod & Nikolaou, 2016; Cousijn et al., 2018) and animal work (Spear, 2018) indicating elevated adolescent alcohol-reward responsiveness, we hypothesized to find a stronger association between alcohol use measures and beer odor cue-reactivity in the Nacc in adolescents compared with adults. If adolescents are more likely to develop AUD, the association between alcohol use measures and beer odor cue-reactivity in caudate, putamen, ACC, and mPFC would be more pronounced in adolescent drinkers. Alternatively, given the preliminary suggestion from animal work that adolescents are less likely to lose control over alcohol use (Fernandez et al., 2017; Labots et al., 2018; Pickens et al., 2019), these associations would be stronger in adults.

MATERIALS AND METHODS

Participants

We recruited 59 adolescent (16 to 18 years) and 54 adult (30 to 35 years) light-to-heavy beer-drinking males closely matched on past-month alcohol consumption in standard units and severity of alcohol use-related problems as measured with the AUDIT (Saunders et al., 1993) via social media and flyers. Recruitment was targeted at drinking frequency/quantity to ensure a homogeneous distribution of low-to-heavy drinkers in both groups. Females and daily smokers were excluded to avoid confounding effects of sex (Melero et al., 2019; Sorokowski et al., 2019) and cigarette smoking (Ajmani et al., 2017) on olfactory processing, and to align the neuroimaging protocol with a parallel study in male rats. Other exclusion criteria were compromised olfactory function, magnetic resonance imaging (MRI) contraindications, a dislike for beer, drug use other than alcohol in the past month, a self-reported history of any mental illness, or current use of psychotropic medication. This was initially verified through a short online screening questionnaire, after which potential participants were contacted by phone to confirm eligibility and make an appointment. On the day of testing, participants with a positive urine screen for recent substance use (cannabis $n = 4$, benzodiazepine and cocaine $n = 1$, cocaine and XTC $n = 1$), deviant sense of smell (Sniffin Sticks Test ≥8; Hummel et al., 1997; $n = 0$), positive alcohol breathalyzer test ($n = 0$), and/or unreliable MRI data (fell asleep $n = 4$, continuous sneezing $n = 1$, technical issues $n = 1$) were excluded. The final sample included 50 adolescents and 51 adults (see Table 1 for sample characteristics). All study protocols were approved by the local ethics committee (2018-DP-8730), and all participants provided informed consent prior to testing.

Assessments of substance use and psychological functioning

Alcohol use disorder was assessed with the MINI version 7.0.0 DSM-5 AUD section (Sheehan et al., 1998) and recent alcohol use during the past 2 weeks in total standard drinks was assessed with the timeline followback procedure adapted from (Martin-Willett et al., 2020). An elaborate history of alcohol use was assessed, including severity of alcohol use-related problems (10-item AUDIT; Saunders et al., 1993), self-reported average monthly drinking days, average drinks per drinking episode, age first drink, age first binge, age first time drunk, and past-year binge drinking episodes. Regarding the use of other substances, lifetime illicit substance use and lifetime cannabis use were assessed.

The 20-item Drinking Motives Questionnaire-revised (DMQ-r) was used to assess social, coping, enhancement, and conformity drinking motives (Cooper, 1994). The 20-item DSM-5 self-rated level 1 cross-cutting symptom measure-adult (DSM-5-CCSM; American Psychiatric Association, 2013), excluding the substance use items, was administered to assess general mental well-being during the past 6 months. Reward responsiveness was assessed with the 8-item Reward Responsiveness scale (Carver & White, 1994), and impulsivity was assessed with the 8-item Barratt Impulsiveness Scale-Brief (BIS-Brief; Steinberg et al., 2013). Intelligence was estimated with the Matrix reasoning subscale of the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2012).

Olfactory alcohol cue-reactivity task

Alcohol (i.e., beer), appetitive control (i.e., grape juice), and neutral "odorless" control (i.e., water) odors were delivered through a nasal cannula connected to an MR-compatible olfactometer that blew air through each solution. The appetitive control odors were included to account for the potential effects of adolescents' increased reward sensitivity on alcohol cue-reactivity. The task contained three blocks of six odor cues (2× beer, 2× grape juice, 2× water) presented for 12 s each (1-s odor ON–1-s odor OFF to prevent habituation), with 18-s wash-out periods between odor cues and a 30-s break between blocks during which a fixation cross was presented. A schematic nose on a black background was presented on screen during all odor presentations, and participants were instructed to breathe normally. An MRI-compatible eye-tracking camera was used to visually verify whether participants remained awake during the task. Total task

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TABLE 1 Sample characteristics.

	Adolescents ($n = 50$)			Adults ($n = 51$)				
	Median	SD	Range	Median	SD	Range	W/t	p
Age	17.0	0.84	16 to 19	31.0	1.64	29 to 35		
AUDIT total	9.5	7.71	1 to 27	8.0	5.73	1 to 22	1411.0	0.356
AUD severity (MINI)	2.0	2.02	0 to 9	1.0	1.99	0 to 8	1496.5	0.125
Monthly use (days)	5.0	6.33	0 to 25	8.0	6.09	0 to 30	1018.5	0.081
Drinks past 2 weeks, TLFB (standard units)	18.3	33.46	0 to 134	24.7	39.23	0 to 198.4	1214.5	0.684
Past-year binge drinking (episodes)	25.0	40.86	0 to 180	15.0	53.63	0 to 200	1369.5	0.409
Drinks per drinking episode (standard units)	4.8	4.64	1 to 25	3.5	3.69	1 to 15	**1600.0**	**0.026**
Age first drink	14.5	1.18	11 to 17	14.0	1.69	10 to 20	1431.0	0.276
Age first binge	16.0	0.93	13 to 17	16.0	1.97	13 to 23	1020.5	0.250
Age first time drunk	15.5	1.06	13 to 17	15.8	2.04	13 to 24	1089.0	0.419
Lifetime Illicit substance (episodes)	0.0	1.86	0 to 13	5.0	34.27	0 to 152	**548.5**	**<0.001**
Lifetime cannabis use (episodes)	6.0	28.78	0 to 120	5.0	169.65	0 to 1000	1211.5	0.794
Drinking motives, DMQ-r								
Social	18.0	4.01	7 to 25	13.0	3.99	6 to 24	**3.80**	**<0.001**
Coping	6.0	2.70	5 to 19	6.0	2.38	5 to 15	1440.4	0.238
Enhancement	15.0	4.30	5 to 22	12.0	4.04	6 to 23	**3.31**	**0.001**
Conformity	5.5	1.87	5 to 14	6.0	2.18	5 to 18	1227.5	0.733
Mental wellbeing, DSM5 CCSM	10.0	8.50	1 to 40	7.0	5.06	1 to 23	1552.5	0.059
Reward Responsiveness	13.0	2.97	8 to 20	14.0	2.85	8 to 19	1.59	0.115
Impulsivity, BIS-Brief	20.0	1.84	15 to 23	19.0	1.79	15 to 24	1490.5	0.137
Intelligence, WAIS Matrix	20.0	3.12	12 to 25	21.0	2.98	9 to 26	1034.0	0.100

Note: Bold values and the exact *p*-values are indicated with < 0.001 for those smaller than that.

Abbreviations: AUD, alcohol use disorder; AUDIT, alcohol use disorder identification test; BIS-Brief, Barratt Impulsiveness Scale-Brief; DMQ-r, Drinking Motives Questionnaire-revised; DSM5 CCSM, Diagnostic and Statistical Manual of Mental Disorder Cross-Cutting Symptom Measure; SD, standard deviation; TLFB, timeline followback; WAIS, Wechsler Adult Intelligence Scale. *p*-values reflect group comparison with independent sample *t*-test or nonparametric Mann–Whitney *U* test (*W*).

time was 10.5 min. To measure craving, we asked before and after the task how much participants felt like drinking beer and juice at that moment with a visual analog scale ranging from "not at all" (0) to "neutral" (50) to "very much" (100). At pre-task, we also asked how much they liked the odors from "not at all" (0) to "neutral" (50) to "very much" (100).

Neuroimaging data collection and preprocessing

Neuroimaging data were collected using a 3 T Philips Achieva MRI scanner and a 32-channel SENSE head coil. A high-resolution structural T1 scan was acquired for registration purposes (TR/TE = 8.5/3.9 ms, FOV = 188 × 240 × 220 mm^3, voxel size = 1 × 1 × 1 mm^3, flip angle = 8°). BOLD signal was measured during the task using a T2* gradient-echo EPI sequence (TR/TE = 2000/28 ms, FOV = 180 × 240 × 240 mm^3, voxel size = 3 × 3 × 3 mm^3, interslice gap = 0.3 mm, flip angle = 76.1°).

Preprocessing was performed using fMRIPrep 1.5.1rc2 (Esteban et al., 2019), which is based on Nipype 1.3.0-rc1 (Gorgolewski et al., 2011). See the Supplementary Methodology for further details about the fMRIPrep preprocessing pipeline.

Data analysis

All presented analyses should be considered explorative given the novelty of the age group comparison.

Sample characteristics, craving, and odor ratings

Statistical analyses were run in JASP (JASP Team, 2019). Sample characteristics were compared between groups with independent *t*-test, nonparametric Mann–Whitney *U* tests for nonnormal data or

chi-square tests. Task-induced craving for beer and juice were compared between adolescents and adults with a repeated-measures ANOVA with cue type (beer and juice) and time (pre-task and post-task) as within-subject factors and age group as between-subject factor. Similarly, odor likings were compared between adolescents and adults with a repeated-measures ANOVA with cue type (beer and juice) as within-subject factors and age group as between-subject factor.

ROI analyses

The evaluation of the preprocessed neuroimaging data did not reveal any remaining motion-related or other data quality issues. General linear model (GLM, ordinary least squares) analysis was subsequently performed using the FMRI Expert Analysis (FEAT) tool version 6.00 of FMRIB's Software Library (Jenkinson et al., 2012). For each odor cue category (i.e., beer, juice, and water), regressors were created by convolving cue onsets and durations (12 s) with a double gamma hemodynamic response function including temporal derivatives. The subtraction contrast Beer > Juice + Water was created to investigate beer odor cue-reactivity, corrected for general appetitive responsiveness. Cortical masks were created by drawing spheres with a 5 mm radius around peak voxel coordinates (*x*, *y*, *z* MNI coordinates: right mPFC = 12, 62, 0; dACC = 0, 2, 34) reported previously (Zeng et al., 2021). Bilateral Nacc, caudate, and putamen subcortical masks were created from high-resolution probabilistic masks thresholded at 0.3 (Pauli et al., 2018). For each mask (n = 8), average percent signal change across all voxels for the Beer > Juice + Water contrast was extracted per participant using Featquery.

For each of the eight regions of interest (ROIs), a series of simple regression models were run in JASP to investigate the simple main effects of AUD (YES/NO), severity of alcohol use-related problems (AUDIT), recent alcohol use in total drinks in the past 2 weeks, past-year frequency of binge drinking, and task-induced craving (post- and pre-craving) on ROI activity, and the moderating role of age group herein (i.e., the interaction between age group (adolescents = 1, adults = 0) and the five alcohol outcome measures). All ROI analyses are presented uncorrected at $p < 0.05$ and corrected for the number of ROIs at $p < 0.0063$ due to the novelty of the age-group comparison. A bootstrapped approach (k = 5000) with 95% confidence intervals was used to control for the stability of the results (i.e., minimize potential effects of influential cases) and account for potential violations in distributional assumptions.

Exploratory whole-brain analyses

Four explorative whole-brain voxel-wise analyses were performed with FEAT mixed-effect higher-level analysis (default $Z < 2.3$, cluster multiple-comparison corrected at $p < 0.05$) to assess the main effects of AUD, drinks past 2 weeks, binge drinking, and craving (all zero-centered) on beer odor cue-reactivity (i.e., Beer > Juice + Water), and the moderating role of age group herein (i.e., the interaction between age group and independent variables).

RESULTS

Sample characteristics, craving and olfactory ratings

Sample characteristics are displayed in Table 1. Onset, frequency and quantity of alcohol use, AUDIT, and AUD severity (symptom count) did not significantly differ between groups; however, adolescents drank more glasses per drinking episode (W = 1600.0, $p = 0.026$) and more adolescents (n = 28) than adults (n = 18) met the cutoff for AUD ($X^2 = 4.36$, $p = 0.037$). Social ($t = 3.79$, $p < 0.001$) and enhancement (t = 3.31, p = 0.001), but not coping and conformity drinking motives, were higher in adolescents than in adults. Mental well-being, reward responsiveness, impulsivity, and estimated intelligence did not significantly differ between adolescents and adults.

Regarding task-induced beer and juice craving, there was a significant main effect of cue type ($F_{1,97} = 36.33$, $p < 0.001$, $\eta^2 = 0.117$), main effect of time ($F_{1,97} = 8.23$, $p = 0.005$, $\eta^2 = 0.008$), main effect of age group ($F_{1,97} = 7.69$, $p = 0.007$, $\eta^2 = 0.030$), and interaction effect between cue type, time, and age group ($F_{1,97} = 13.79$, $p < 0.001$, $\eta^2 = 0.007$). Beer craving was significantly lower than juice craving at both time points in both groups (all $ps < 0.012$; Figure 1A). Comparing pre-task and post-task craving within groups, adolescents showed an increase in beer craving ($t = 4.95$, $p < 0.001$, $d = 0.71$) while adults showed an increase in juice craving (t = 2.10, p = 0.041, d = 0.29). Compared with adults, adolescents showed higher juice cravings (pre-task: $t = 3.61$, $p < 0.001$, $d = 0.72$; post-task: $t = 2.45$, $p = 0.016$, d = 0.49) and higher post-task beer craving (t = 2.16, p = 0.033, $d = 0.43$).

Regarding the liking of the beer and juice odors, there was a significant main effect of age group ($F_{1,97} = 6.38$, $p = 0.013$, $\eta^2 = 0.035$), but no main effect of cue type ($F_{1,98} = 3.00$, $p = 0.086$, $\eta^2 = 0.013$) or interaction effect between cue type and age group ($F_{1,98} = 0.20$, $p = 0.654$, $\eta^2 = 0.000$). Adolescents liked the odors better, the group effect mainly being driven by higher liking of the beer odor in adolescents versus adults (beer: t = 2.16, p = 0.033, d = 0.43; juice: $t = 1.64$, $p = 0.104$, $d = 0.33$; Figure 1B).

ROI analyses

There were no significant main effects of age group, AUD, AUDIT, total drinks in the past 2 weeks, binge drinking, and task-induced craving on ROI activity (See Table S1 for all simple and moderation effects). Age moderated the relation between AUD and beer odor-induced activity in the right caudate ($B = -0.075$, $B_{se} = 0.034$, $\beta = -0.68$, $t = -2.23$, $p = 0.028$, 95% bca CI [−0.137, −0.014]). Post hoc comparisons in this region revealed higher beer odor-induced activity in adolescents with AUD versus those who did not ($t = 2.59$, p = 0.013, Cohen's d = 0.74; Figure 2A), which was not the case

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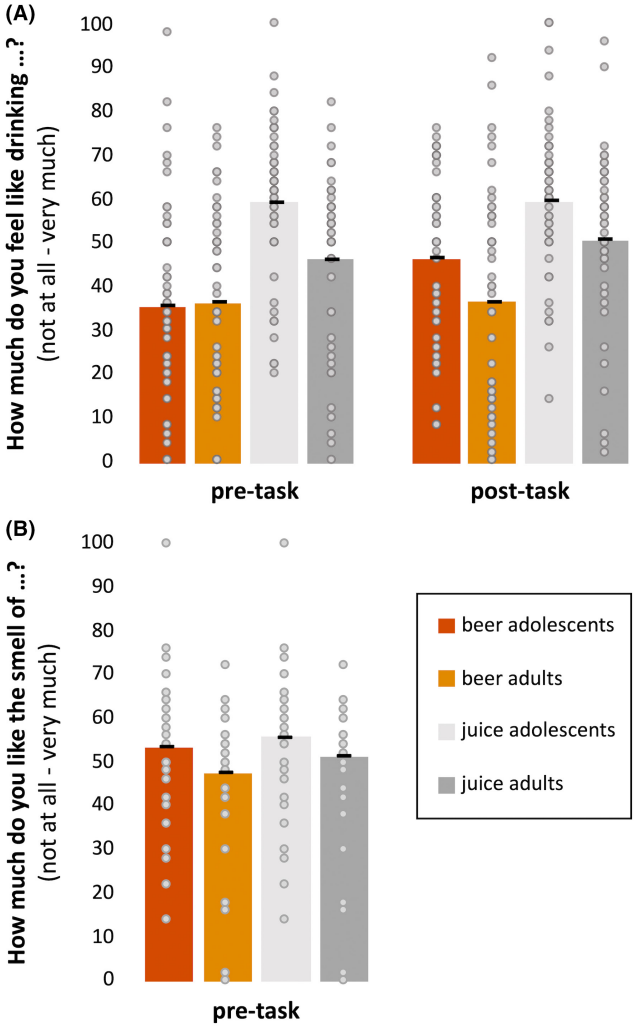

FIGURE 1 (A) Beer and juice craving pre- and post-olfactory cue exposure task in adolescents and adults. Significant (all *p*s <0.05) within group pre-to-post increase in beer craving in adolescents and juice craving in adults. Both adolescents and adults displayed higher juice than beer craving at pre-task and post-task. Comparing groups, higher pre-task juice, post-task juice, and post-task beer craving in adolescents versus adults. (B) Beer and juice odor liking pre-olfactory cue exposure task in adolescents and adult. Significant main effect of group ($p = 0.013$), driven by higher beer odor likings in adolescents versus adults ($p = 0.033$). Means and individual data points are depicted.

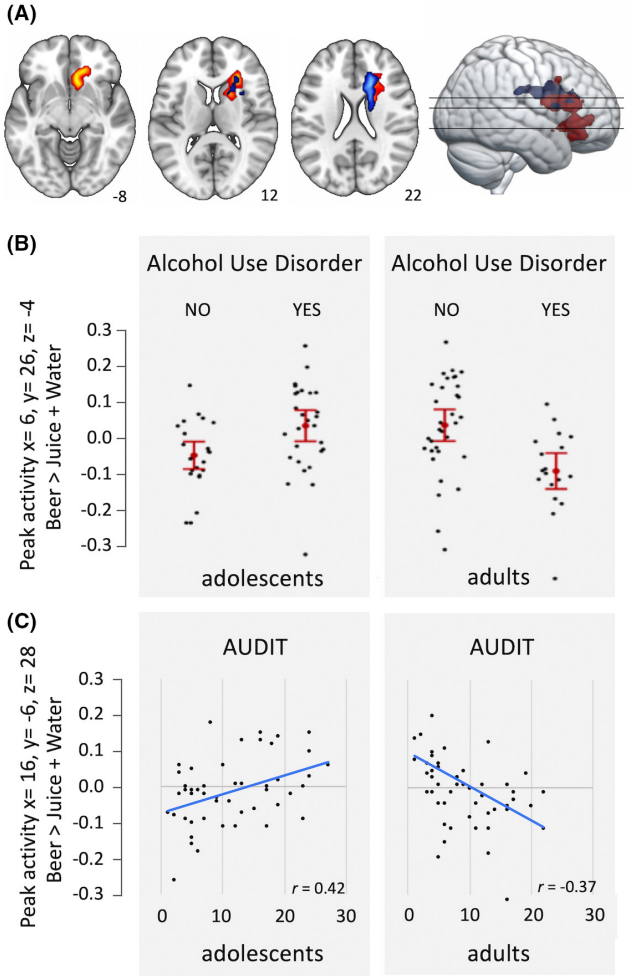

FIGURE 2 (A) Whole-brain analysis ($Z > 2.3$, cluster-corrected $p < 0.05$) showed overlapping mesocorticolimbic clusters in which age group significantly moderated the association between beer odor-induced activity (Beer > Juice + Water) and alcohol use disorder (AUD YES/NO; red) and the alcohol use disorder identification test (AUDIT; blue). (B) Post hoc analysis of extracted peak activity (percent signal change) showed higher beer odor-induced activity in adolescents with AUD versus adolescents without AUD ($t = -2.57$, $p = 0.035$) and adults with AUD ($t = -2.70$, $p = 0.033$). Standard error intervals are displayed in red and dots represent individual data points. Moreover, (C) there was a positive association between activity and AUDIT scores in adolescents ($r = 0.42$, $p = 0.002$) and a negative association in adults ($r = -0.37$, $p = 0.007$).

in adults ($t = 0.64$, $p = 0.528$, Cohen's $d = 0.18$). However, this effect did not survive a stricter multiple comparison correction for the number of ROIs tested. Age group did not significantly moderate the association between alcohol outcomes and beer odor-induced activity in the left caudate, bilateral putamen, bilateral Nacc, and mPFC.

Exploratory whole-brain analyses

There were no significant main effects of age group, AUD, AUDIT, total drinks in the past 2 weeks, binge drinking, and task-induced craving on beer odor-induced activity. Age group significantly moderated the association between AUD and beer odor-induced activity in a large cluster of voxels encompassing the right caudate, Nacc, orbitofrontal cortex, and the olfactory sulcus ($Z > 2.3$ cluster corrected at $p < 0.05$; 1748 voxels; $Z_{max} = 4.5$; mni coordinates peak voxel: $x = 22$, $y = 28$, $z = -14$; Figure 2A). Post hoc analysis (Holm–Bonferroni corrected) of extracted peak activity showed higher beer odor-induced activity in adolescents with AUD versus adolescents without AUD ($t = -2.57$, $p = 0.035$) and adults with AUD ($t = -2.70$, $p = 0.033$). Age group also significantly moderated the association between AUDIT and beer odor-induced activity in an overlapping

cluster encompassing the right caudate and putamen ($Z > 2.3$ cluster corrected at $p < 0.05$; 1748 voxels; $Z_{max} = 4.3$; mni coordinates peak voxel: $x = 16$, $y = -8$, $z = 28$; Figure 2A). Post hoc analysis showed a positive association between activity and AUDIT scores in adolescents ($r = 0.42$, $p = 0.002$) and a negative association in adults ($r = -0.37$, $p = 0.007$). Age group did not significantly moderate any of the other associations between alcohol outcomes and brain activity.

DISCUSSION

This study compared behavioral and neural alcohol cue-reactivity between adolescent and adult drinkers. In contrast to juice cravings, beer cravings increased over the course of the olfactory cue-exposure task in adolescents only. Individual differences in recent alcohol use (total drinks past 2 weeks), past-year frequency of binge drinking, and task-induced craving did not relate to beer odor-induced neural activity in the ROI and whole-brain analyses. However, whole-brain analysis indicted that adolescents that met the DSM-5 criteria for AUD showed higher beer odor-induced activity in a large mesocorticolimbic cluster of voxels encompassing the right caudate, Nacc, orbitofrontal cortex, and the olfactory sulcus compared with adolescents without AUD and adults with AUD. Moreover, in an overlapping cluster including the caudate and putamen, beer odor-induced activity increased with increasing severity of alcohol use as measured with the AUDIT in adolescents, but decreased with increasing severity in adults. These mesocorticolimbic areas have been shown to play an important role in AUD development and maintenance (Cofresí et al., 2019; Vollstädt-Klein et al., 2010; Zeng et al., 2021).

We explored the association beer-odor induced activity and different facets of problematic alcohol use. Our results suggest that age may impact the processes underlying craving and severity of alcohol use-related problems. The associations between frequency measures of alcohol use and beer odor-induced activity did not differ between adolescents and adults. These results should be considered preliminary, also given the relatively low capacity of the beer odors to evoke craving and neural cue-reactivity in adults. Nevertheless, the adolescent-specific increase in beer craving and positive association between severity of alcohol use and activity in mesocorticolimbic areas may suggest adolescent risk rather than resilience. This is further supported by significantly more adolescents meeting the cutoff of AUD, despite adolescents and adults starting drinking at a similar age, currently drinking similar amounts of alcohol, and adults having higher cumulative exposure to alcohol. Post hoc analyses comparing the adolescents and adults that met AUD (Table S2) also revealed no significant differences in any of the alcohol use measures between age groups. Adolescents with AUD scored lower on the WAIS IQ matrix reasoning subtest ($t = 2.30$, $p = 0.026$), but correcting for this did not influence the findings. Post hoc exploration of individual AUD symptoms revealed that the group difference in AUD prevalence was driven by adolescents scoring more frequently positive for past-year tolerance ($n = 30$) than adults ($n = 17$; $X^2 = 7.216$, $p = 0.007$). Age-related differences in alcohol metabolism may play a role in this since animal studies suggest reduced sensitivity to alcohol's intoxicating effects during adolescence (e.g., Marshall et al., 2020). The higher juice craving, increase in beer craving and higher liking of the beer odors in adolescents support the normative heightened appetitive/reward sensitivity generally observed in this age group (Conrod & Nikolaou, 2016; Cousijn et al., 2018). Moreover, drinking to increase social connections and enhance positive affect was also more prevalent among adolescents compared with adults. Interestingly, while both adolescents and adults most commonly reported drinking for social reasons (Kuntsche et al., 2005), the maturational reductions in problem drinking towards adulthood have been linked to decreases in enhancement motives (Littlefield et al., 2010).

In adults, alcohol cue-reactivity in mesocorticolimbic areas has been found to predict escalation of use (Dager et al., 2014) and relapse (Bach et al., 2015; Grüsser et al., 2004; Reinhard et al., 2015), and to consistently decrease after treatment (Zeng et al., 2021). The few studies that investigated neural alcohol cue-reactivity in adolescents report similar results, with elevated mesocorticolimbic cue-reactivity in adolescents with AUD compared to those without AUD (Tapert et al., 2003) and reduced cue-reactivity after abstinence (Brumback et al., 2015). Elevated striatal activity during tasks containing a motivational/reward component has also been observed before the onset of drinking in children/adolescents at-risk of AUD (Tervo-Clemmens et al., 2020). Considering alcohol cue-reactivity specifically, a longitudinal neuroimaging study showed that differences in activity between adolescents with and without a family history of AUD only emerged after the onset of heavy drinking (Nguyen-Louie et al., 2018). Integrating these findings with our own, preexisting risk factors and the severity of drinking may both contribute to elevated alcohol cue-reactivity and the development of alcohol cue-reactivity may be facilitated in adolescents versus adults.

In contrast to our hypothesis, we did not observe an association between any of the alcohol outcomes and beer odor-induced activity in the mPFC and ACC, two areas generally more active during cue exposure tasks in adults with AUD compared with adults without AUD (Zeng et al., 2021). Many factors are known to influence neural cue-reactivity, including but not limited to AUD severity, craving, abstinence, withdrawal, treatment status, and sensory cue modality (for an overview, see Jasinska et al., 2014). Our sample consists of low-to-severe drinkers from the general population with a preference for beer. Looking at previous fMRI studies using an olfactory paradigm specifically, odor-induced activity patterns are inconsistent, with most studies including small samples of 10 to 30 heavy drinkers (Bragulat et al., 2008; Kareken et al., 2010; Oberlin et al., 2012) or AUD patients (Lukas et al., 2013). Only two of these studies compared heavy drinkers (Kareken et al., 2004) or AUD patients (Schneider et al., 2001) with controls, each including 10 or fewer participants per group. Behavioral data show that alcohol odors are capable of eliciting craving in AUD patients (Reid et al., 2006; Schneider et al., 2001). However, the lower beer-relative-to-juice craving scores, the beer

craving and liking scores being below or around 50 (i.e., neutral), and the absence of increased alcohol cue-reactivity in mesocorticolimbic areas in the full sample indicate a generally low appetitive value of the beer odors in our participants. While the use of beer odors may have been powerful enough to detect differences between adolescents with AUD and without AUD, it may not be powerful enough for the detection of more subtle relationships between alcohol use and cue-reactivity in community samples of low-to-heavy drinkers. Next steps would include comparing beer-odor cue-reactivity between more severe groups of adolescent and adult AUD patients in treatment relative to a low-drinking control group. Regarding cue type, although visual alcohol cues are most often used, multisensory cues are thought to elicit more robust patterns of brain activity (Yalachkov et al., 2012). We specifically developed an olfactory cues paradigm that could be used in humans and rodents to enable the development of a translational research line. However, combining sensory dimensions (e.g., olfactory and visual) would be recommended to optimize the cue-reactivity paradigm. Also, given the greater role of social processes in adolescent versus adult drinking (Cousijn et al., 2018), the comparison between social and nonsocial alcohol cues may further uncover clinically relevant similarities and differences between adolescent and adult AUD (Groefsema et al., 2020).

A clear strength of this study is the direct comparison between adolescent and adult drinkers closely matched on different measures of alcohol use. However, some limitations should be considered. First, we excluded females in this first study to avoid potential confounding effects of sex on olfactory processing (Melero et al., 2019; Sorokowski et al., 2019). Alcohol cue-reactivity is suggested to be stronger in males (Kaag et al., 2019) but general odor cue-reactivity in the brain seems to be larger in females (Yousem et al., 1999). Second, adults have cumulatively consumed more alcohol over a longer period of time. We tried to minimize differences in alcohol exposure between groups by matching groups on current frequency of alcohol use and severity of alcohol use-related problems (i.e., AUDIT). Higher neural alcohol cue-reactivity in adolescents with AUD, increasing neural alcohol cue-reactivity with increasing severity of alcohol use-related problems, and higher task-induced beer craving in the adolescent group as a whole may suggest a minimal confounding role of exposure duration in these results; however, this cannot be confirmed with the current design. Given the strong correlation between age and exposure duration, correcting for exposure duration would remove valuable variance related to age. To further investigate this, future studies could compare adolescents and adults matched on cumulative alcohol exposure rather than recent exposure. Third, we included a limited age range and drinkers from the general population. It should be tested whether the results translate to younger and older age groups and clinical populations. Finally, our cross-sectional design precludes causal inferences. To further unravel the role of age, future studies are therefore encouraged to include a wider age range of both males and females, test cue-reactivity beyond one sensory modality, and employ a longitudinal design in both clinical and nonclinical populations. Moreover, efforts to harmonize cue-exposure protocols (Ekhtiari et al., 2022) will likely improve alcohol cue-reactivity research and increase the potential value of cue-reactivity as a clinical biomarker (Verdejo-Garcia et al., 2019).

In conclusion, adolescents with AUD compared with adolescents without AUD and adults with AUD showed higher beer odor-induced activity in a large mesocorticolimbic cluster encompassing the right caudate, nucleus accumbens, orbitofrontal cortex, and the olfactory sulcus. Moreover, activity in a cluster containing the right caudate and putamen was positively associated with severity of alcohol use-related problems in adolescents but negatively in adults. Beer craving also increased over the course of the olfactory cue-exposure task in adolescents only. These findings suggest a differential role of alcohol cue-reactivity in adolescent versus adult AUD, highlighting the urgency for studies investigating similarities and differences in the processes underlying the maintenance and recovery of AUD across different age groups.

AUTHOR CONTRIBUTIONS

JC, GM, MD, IG, and HL were responsible for the study concept and design. JC, IW, and HL acquired the funding. GM and NR recruited the participants and collected the data. JC performed the data analysis and all authors assisted in the interpretation of the findings. JC drafted the manuscript and all authors critically reviewed content and approved the final version for publication.

ACKNOWLEDGMENTS

This work was supported by an Amsterdam Brain and Cognition 2017 Project grant awarded to JC, IW, and HL, and by an ERC starting grant (947761 Aging Matters) awarded to JC. We would like to thank Emese Kroon, Lorraine Minnaar, Cece Kooper, and Amber de Haas for their help with data collection. The authors declare that there are no conflicts of interest.

CONFLICT OF INTEREST STATEMENT

None.

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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cousijn, J., Mies, G., Runia, N., Derksen, M., Willuhn, I. & Lesscher, H. (2023) The impact of age on olfactory alcohol cue-reactivity: A functional magnetic resonance imaging study in adolescent and adult male drinkers. *Alcohol: Clinical and Experimental Research*, 47, 668–677. Available from: https://doi.org/10.1111/acer.15037